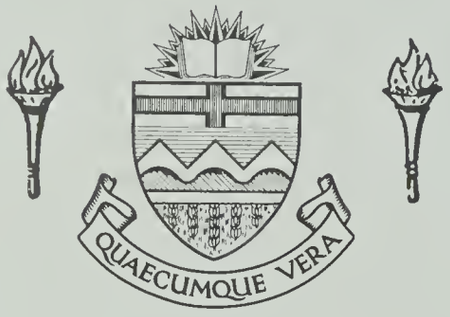

THE UNIVERSITY OF ALBERTA

PUMP-OXYGENATOR BLOOD FLOW DISTRIBUTION DURING RESPIRATORY DISTRESS

by

Donald Edward James

A THESIS

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The undersigned certify that they have read and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Pump-Oxygenator Blood Flow Distribution During Respiratory Distress", submitted by Donald Edward James, in partial fulfillment of the requirements for the degree of Master of Science (Surgery).

ABSTRACT

An understanding of distributional blood flow during partial cardiopulmonary bypass by conventional methods is essential in a study of respiratory distress treated by these techniques. Despite this, the actual distributional patterns, particularly the total cerebral flow, is unknown during partial cardiopulmonary bypass. The purpose of our experiment was to establish therefore, distributional flow patterns during partial cardiopulmonary bypass as assist for respiratory distress.

Asphyxia was induced in mongrel dogs by means of airway restriction with partial cardiopulmonary bypass being instituted at a point when the animals arterial oxygen tension, numerically, fell below that of the arterial carbon dioxide tension. This point we have defined as "crossing" and due to its predictability regarding survival without cardiopulmonary assist, feel it should be used in all studies of oxygenator assessment.

Blood from the inferior vena cava supplied the pump-oxygenator system and was returned to the animal in either femoral artery, axillary artery, aortic root, (veno-arterial bypass) or external jugular vein (veno-veno bypass) vessels. Cerebral tissue pO_2 responses were monitored during asphyxia and during partial cardiopulmonary bypass. Further studies were performed using a cardiodensitometer to detect the distribution of pump-oxygenator blood which had been previously labelled with Cardio-green dye.

Oxygen microelectrode studies show a continual decline in cerebral tissue pO_2 tension with asphyxia with little alteration, if any, of the decreasing cerebral tissue pO_2 tension with partial extracorporeal circulation utilizing a femoral artery return. The absence of pump-oxygenator blood distribution to the cerebrum, as evidenced by the continual decrease in cerebral tissue pO_2 tension is confirmed by Cardio-green dye distribution studies.

Axillary artery return halts the decline of cerebral tissue pO_2 associated with asphyxia and produces a marked and immediate rise shortly following initiation of partial extracorporeal oxygenation as assist. The hemodynamics surrounding these responses are seen in the dye distribution studies.

Cerebral tissue pO_2 tension responses and Cardio-green dye distribution studies result in similar responses with either an aortic root or external jugular vein return of a partial cardiopulmonary bypass circuit. Improvement in cerebral tissue perfusion is noted with the pump-oxygenator system although the response is not as immediate as that for an axillary artery return route. The ultimate response which is similar to that of the axillary artery return is delayed in time. , Veno-veno bypass with an external jugular vein return route may be more favourable in long term perfusion to that of the aortic root return due primarily to factors influencing hemolysis.

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PUMP-OXYGENATOR BLOOD FLOW DISTRIBUTION DURING RESPIRATORY DISTRESS

A. Hemodynamic Aspects of Partial Cardiopulmonary Bypass

It has been stated by Galletti (68) that, "when gas exchange and blood pumping occur simultaneously in the natural organs and artificial devices, the hemodynamic and metabolic conditions are far more complex than those during the complete substitution of the heart and lungs". It was only a few years ago that many workers considered hazardous the intermediate period of partial heart-lung bypass which immediately precedes and follows total heart-lung bypass. Rather than attempting to manage this state of competition between the heart and pump-oxygenator, they preferred to make the partial bypass period as short as possible, and face the relatively well understood problems of either total body perfusion or normal circulatory conditions.

Galletti and others (67,69,70,92) and Salisbury et al (159,160) have investigated the effects of partial heart-lung bypass on vascular pressures and flows. The complex inter-relationships between extracorporeal flow rate, cardiac output and body blood volume, can be summarized as follows:

1. With a constant body blood volume, cardiac output varies inversely with extracorporeal flow rate.

2. If body blood volume remains constant blood will shift from the organism into the external circuit as the extracorporeal flow rate increases and shift back into the vascular system as the rate of partial perfusion is diminished.

3. The perfused animal is extremely sensitive to variations in blood volume, reacting markedly to small transfusions or withdrawals which would barely affect the normal circulatory system.

4. Arterial pressure reflects changes in total perfusion (cardiac output plus extracorporeal flow). When extracorporeal flow is modified without changes in the body blood volume, and thus without changes in the total perfusion flow, mean aortic pressure remains constant regardless of the relative sizes of the left ventricular and pump-oxygenator contributions. The pulse pressure decreases with decreased cardiac output. The mean central venous pressure is slightly decreased by increases in extracorporeal flow. Right ventricular systolic pressure and pulmonary arterial pressure are consistently and progressively diminished with increments of size in extracorporeal flow which correspond to decrements in pulmonary blood flow. Left atrial pressure is always significantly decreased when the bypass circuit carries more than 25 percent of the total perfusion flow.

5. There is no evidence of vasomotor activity when the total perfusion flow rate is constant, although the relative contributions of the left ventricle and of the heart-lung machine are varied.

6. Sludging of red cells and blockage of capillary networks can sometimes be reversed by partial cardiopulmonary bypass presumably because of the higher head of pressure provided at the arterial level (17).

7. The heart rate slows as more blood is carried by the extracorporeal circuit. This relative bradycardia is associated with a fall in central venous pressure and in right ventricular pressure and

may be interpreted as an extended "Bainbridge effect". Conversely, the heart rate usually accelerates when pulmonary blood flow and, as a result, cardiac output is permitted to increase as extracorporeal flow rate decreases. Since there is no concomitant change in arterial pressure, the change in heart rate cannot be ascribed to a carotid sinus mechanism. Changes in heart rate are not consistently observed in open-chest animals, nor in those which are deeply anesthetized.

8. When partial heart-lung bypass brings about a reduction in cardiac output out of proportion to the decrease in heart rate, the left ventricular pressure pulse tracing often shows mechanical alternation. Alternate left ventricular systoles show no ejection phase. Aortic pressure remains constant during the ineffective systole and consequently the aortic pulse pressure is reduced to one-half. There is no change in the electrocardiographic sequence nor in the right ventricular pressure pattern. Left ventricular mechanical alternation is noted when the stroke volume of the right ventricle is insufficient to fill the left ventricle after passage of blood through the pulmonary vascular bed. Two contractions of the right ventricle are needed to pump enough blood into the left heart cavities to bring about left ventricular ejection. It is not of especially ominous significance, although it does warn that total perfusion flow may be too low.

9. Partial heart-lung bypass is not associated with electrocardiographic changes other than bradycardia. Although not related to the perfusion, bradycardia may be caused by myocardial hypoxia, hyper-

kalemia, right ventricular overload, marked temperature variations or mechanical stimulation by intracardiac catheters.

10. Myocardial oxygen consumption is not consistently affected by the redistribution of total systemic flow between the left ventricle and the extracorporeal circuit. When extracorporeal flow is more than 50 percent of the total perfusion flow, myocardial oxygen consumption will sometimes decrease although it may remain constant as long as there is any left ventricular output.

11. There is no agreement as to the effects of partial heart-lung bypass upon the work of the heart.

B. Experimental and Clinical Experiences

The concept of partial perfusion or of supplementing the normal circulation by an external "parallel circulation" was originally introduced by Brukhonenko (23) in 1929. Circulatory assistance by pump oxygenator was first considered as an aid to surgery in order to support cardiac patients who otherwise would not have been able to withstand operation (2,57) and since the early reports by Dogliotti (55-57) and Constantini et al, (38) of the clinical application of partial heart-lung bypass, experimental attempts have been carried out in Italy to resuscitate animals subjected to drowning, electric shock or carbon monoxide poisoning (46-48).

Other workers (80,105,171) have reported the successful use of partial heart-lung bypass in patients suffering from pulmonary edema and acute myocardial infarction. Bor et al (18) and Bor and Rieben (17) found that symptoms of induced heart failure in dogs could be corrected by an appropriate selection of flow and pressure conditions.

Others (174) were unable to reverse any aspect of the clinical picture of chronic congestive failure in animals with a similar veno-arterial bypass. Beneficial effects proportional to the extracorporeal flow rate was noted in dogs made hypotensive by spinal anesthesia (180).

Endotoxic shock has been used to test the efficacy of assisted circulation; here, decreased venous return and fall in cardiac output are primary circulatory disturbances (179) and afford an ideal test for assist. Bor et al (19) noted a clear reversal of the hemodynamic signs associated with endotoxic shock following the use of partial cardiopulmonary bypass. Other non-surgical cases in which partial cardiopulmonary bypass has been used is during renal and hepatic failure (158) and also for the sole purpose of respiration (85) or circulatory assistance (135).

More recently, most attempts both clinical and experimental, have been directed toward the temporary relief of the failing heart and to assist oxygenation in acute or chronic pulmonary problems associated with the sudden onset of clinical states severely hampering an already limited pulmonary gas-exchange system. These reports of assisted circulation techniques in man are still scanty (52,82,99,138,139,149, 169,171,176).

C. Problems Associated with Long Term Partial Cardiopulmonary Bypass

As the surgical correction of increasingly complex cardiac lesions led to longer perfusions some of the limitations of the various bubbling, screening and filming devices became obvious. It was found that survival was rare when perfusion time exceeded five to six hours (74).

One aspect common to all oxygenators used were large blood-gas interfaces. Since nowhere in the plant or animal kingdom are respiratory gases allowed to mix directly with transporting fluids, methods attempting to duplicate nature's systems and utilizing plastic membranes (non-viable and non-wettable) have been employed. These necessitate interaction on the surface of the membrane that may impart harmful energy to the blood. Nevertheless, advantages are offered because available plastic membranes decrease the destruction of the blood elements when blood and gases are mixed (45). Extensive studies have been performed on membranes of varying types, studying their gas transference capabilities (31,32,45,62,104,122,124,146,148,152) and other factors influencing oxygen uptake of the blood such as stationary boundary layers and turbulence (6,119,120).

Devices for assisted circulation must be reliable for continuous use for days to weeks, depending upon the need of the patient. Any artificial pump-oxygenator system has direct contact with the blood resulting in some destruction of blood elements. The foreign surfaces of the extracorporeal circuits (170), turbulence (181) and shearing forces (60,125), blood-gas interfaces, and nonphysiologic handling of blood by pumps (10,11,12,22,84,88,101,121) combine to produce damage to the cellular elements of the blood (68) with disturbance of bodily circulatory, metabolic and regulatory mechanisms (68). The effects include platelet aggregation, and other white and red blood cell aggregations, blood sludging, microembolism (115,157,173), fat embolism (1,141,183), hemolysis (113,151), anemia (11,66,96,106,107), induced hypercoagulability and intravascular thombosis (59,71,72,117,185), damage to lungs (9,61,66,134,166,175) and kidneys (54,131), and the

release of toxic products by the destruction of cellular elements of the blood (63). These toxic products embrace vasoactive substances such as histamine (37,90,150), serotonin (90,155,177), "kinins" (4) produced by fibrinolysin, and other vasoactive poly-peptides and toxic materials formed by the action of over a dozen proteolytic and hydrolytic enzymes released from the broken-down lysosomes (171) of the destroyed white blood cells. Still other metabolic changes during perfusion are the increased production of catecholamines (122,155), acidosis (8,68,77), electrolyte shifts (68) and water retention and intravascular pooling (66,68,114).

Since circulatory assistance can be applied for short periods only, its use is limited to pathological states that are potentially reversible. Generally it should be reserved for cases in which all avenues of conservative treatment have been exhausted. It is not uncommon to encounter clinical situations in which a primary hemodynamic effect leads to metabolic disturbances which, in turn, detrimentally affects the function of the circulatory system. When such a vicious cycle becomes established, interruption by drugs or other conventional means is often impossible. Mechanical assistance to the circulation can then be advised as a powerful measure for tiding the patient over a transient period of cardiorespiratory failure. Mechanical pumping and/or extracorporeal gas-exchange provide the support needed while the underlying process responds to conventional treatment, or until the affected function recovers spontaneously.

D. The Effects of Partial Cardiopulmonary Bypass on Body Organs

Partial heart-lung bypass involves not only circulation and gas exchange which are of fundamental concern, but it also affects all other processes which may be modified by a redistribution of blood flow, such as the cerebral, renal and thermoregulatory functions. Consequently, before being able to recommend heart-lung bypass as a therapeutic procedure, the side effects must be thoroughly investigated in the normal and abnormal organism.

1. Lungs. With a reduction in pulmonary blood flow, spontaneously breathing dogs ventilate less and because the decrease in ventilation is not so great as the decrease in blood flow a relative hyperventilation results.

2. Brain. Cerebral blood flow is probably well maintained in the presence of normal aortic and low venous pressures. No direct measurements of cerebral blood flow have been reported, nor has brain tissue oxygen tension been systematically investigated.

3. Kidney and Body Fluids. Where there is no evidence of transfusion reaction and mean aortic pressure is adequately maintained, urine output during bypass remains in the range observed under anesthesia in the hour preceeding bypass. Urine specific gravity is not altered significantly. Extracellular fluid volume and total body volume and total body water are consistently augmented immediately after perfusion and for a period of twelve hours thereafter. Then, a massive diuresis eliminates water retained in the animal (67).

Interestingly enough, animals perfused by means of gravity do not exhibit as marked an increase in weight after perfusion as do animals perfused at the same flow rate by means of an occlusive roller pump. No explanation has been given for this phenomenon.

4. Liver and Gastrointestinal Tract. Little or no data is available on any modifications of liver function during partial cardiopulmonary bypass. Hypoglycemia after 10-15 hours of perfusion in the dog may reflect a disturbance of hepatic function. A rise of portal venous pressure at the onset of perfusion was reported by Dow et al (55) and found to be associated with the anaphylactoid reaction of massive blood transfusion. Gastrointestinal bleeding occasionally occurs after perfusion, but its pathogenesis is not known.

5. Blood Elements. The traumatic destruction of all blood elements has remained, to the present, one of the problems of long-term partial cardiopulmonary bypass. These effects have been previously discussed.

E. Techniques of Partial Cardiopulmonary Bypass

The techniques that may be employed for providing long-term support depend on whether the pathological problem is circulatory, respiratory, or both. The techniques include:

1. Veno-arterial pumping with or without oxygenation (36,136, 142).
2. Right or left ventricular bypass (49,161).
3. Arterial counterpulsation (30,167).
4. Oxygenation via veno-veno bypass (176).

5. Oxygenation via arteriovenous bypass (68).

6. External body compression (168).

The controversial aspects of these techniques have been published (8,68,164,169).

Techniques aimed either at hemodynamic or metabolic assistance alone are often incapable of relieving the complex disturbance characteristic of heart and circulatory failure for prolonged periods. The reason for this is that one must be able to supplement, to varying degrees, the respiratory as well as the circulatory failure of the patient. Often the degree of support required changes independently for each function. Therefore, only a circuit which offers extracorporeal gas exchange together with hemodynamic support can be considered truly satisfactory. Ideally, the most beneficial conditions for circulatory assistance are provided by partial heart-lung bypass, or "parallel blood circulation", as it was originally called by Brukhonenko in 1929.

F. Methods of Producing Respiratory Distress

Many changes have occurred in the field of partial cardiopulmonary assist, from the improved technological designs (13-16,20,34,40,44,64,74,89,100,102,116,139,143-145,147) of artificial lungs to the extensive investigation of various physiologic parameters, but many areas for fruitful investigation remain. With the appearance of many newer designs in membrane oxygenators, it is noted, with some dismay, that no universal criteria exists for the laboratory assessment of blood-gas exchange apparatus capabilities during mimicked respiratory distress.

This distress has been produced in a number of ways, most notably by sub-total airway obstruction (98,176), by allowing animals to breathe spontaneously 5-10% oxygen in nitrogen mixtures (26) or by producing venous desaturation by reducing the ventilation of animals on room air (111) that is, a reduction in minute volume.

In other instances, assessment of oxygenator function is made with animals on partial cardiopulmonary bypass and breathing spontaneously throughout the perfusion period from a closed circuit spirometer filled with pure oxygen (91) or room air (66). Many of these latter methods of assessment, it must be admitted, are valid in that they evaluate the animals tolerance to prolonged procedures. The performance of extensive hematologic and metabolic studies during these methods help elucidate some of the factors which often limit the duration of perfusion procedures.

The problem that arises is not the method of producing respiratory distress for the final result is the same, that is a change in the blood-gas picture with associated metabolic and acid-base disturbance and ultimate death, but one of when shall partial cardiopulmonary bypass be started. Partial cardiopulmonary bypass assist should be initiated when it has some clinical significance and predictability as to the outcome.

Techniques thus far used have involved partial cardiopulmonary bypass on dogs breathing normally, or in those in which partial cardiopulmonary bypass was instituted at the time of initiating respiratory distress. These methods have very little clinical significance or predictability. Because of this, the first part of this study was

involved with the seeking of a point in respiratory distress which could serve as a point to initiate pump-oxygenator assist.

The limited capacity of our membrane oxygenator made its evaluation necessary in order that any studies being carried out were done so during a period when the membrane oxygenation was functioning adequately. These studies concerned the distribution of pump-oxygenator blood during bypass utilizing a number of pump-oxygenator return sites. Both direct and indirect methods were used to study this. The direct method involved the labelling of blood from the pump-oxygenator with dye which could be detected by means of a cardiodensitometer. The indirect method was that of measuring the cerebral tissue pO_2 response to various bypass re-entry sites.

The purpose of the study may be outlined as follows:

A. The Establishment of a Cardiopulmonary Bypass Assist Point.

B. Membrane Oxygenator Assessment.

C. Pump-Oxygenator Blood Distribution Studies.

   1. Cerebral tissue pO_2 responses.

   2. Pump-oxygenator and cardiac dye distribution studies.

CHAPTER II

METHODS AND APPARATUS

A. The Establishment of a Cardiopulmonary Bypass Assist Point

Ten mongrel dogs, weighing 9.5 to 15.5 kilograms, were used as controls. The only anesthesia given consisted of sodium pentobarbital given intravenously in a dose of 30 milligrams per kilogram body weight. A femoral artery was cannulated for blood-gas sampling following the insertion of a cuffed endotracheal tube. Heparinization consisted of 3 mg./kg. body weight initially and 1 mg./kg. hourly thereafter.

Blood gas determinations included pCO_2, pO_2 and pH performed on a Radiometer Copenhagen gas analyzer. After an initial withdrawal of 10 cc. blood, a second sample of 4 cc. was used for the gas determinations. All blood was then returned to the animals. Blood-gases were determined at one-half and one hour after induction of anesthesia. At the latter point the airway was obstructed by a #14 needle inserted into the lumen of the endotracheal tube. No intravenous fluids, bicarbonate or medications were given. Blood-gas sampling was done every ten minutes with the gas analysis being done immediately. If the animals were not distressed, the period between blood-gas samples was gradually increased and sampling continued to death.

B. Membrane Oxygenator Assessment

Eleven mongrel dogs, weighing 10.5 to 16.5 kg. were placed on partial cardiopulmonary bypass utilizing the membrane oxygenator of Peirce.

The oxygenator consists of a number of rubber mats stacked upon each other. Between these mats is laid down a double layer of 0.5 mil. teflon membrane (Figure 1). Between the layers of teflon, at diagonal

Figure 1. Shown is one stage in the assembly of the membrane lung. Note the successive layers of rubber mats between which can be seen the teflon membranes.

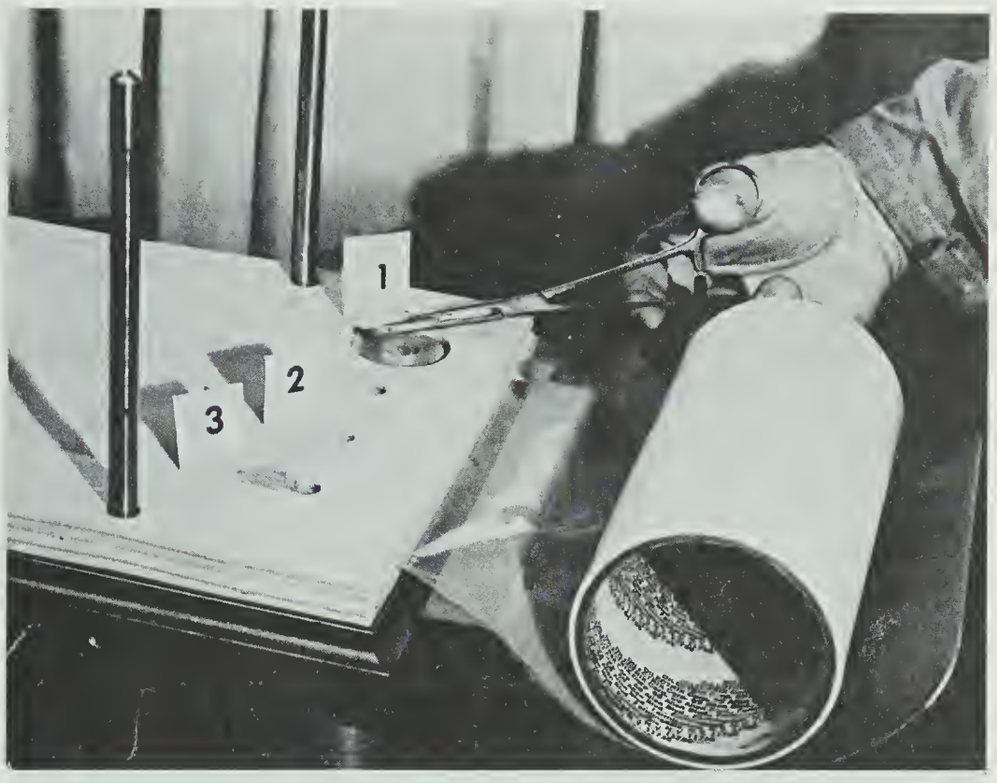

Figure 2. Shown is the blood distribution disc (1) overlaying the blood inlet column. A clear oxygen distribution plug (3) is seen at the opposite corner in the oxygen outlet column (counter current flow). (2) represents a blank insert as this column is not used in the lung setup. The roll of double layered teflon is seen sitting in a cradle.

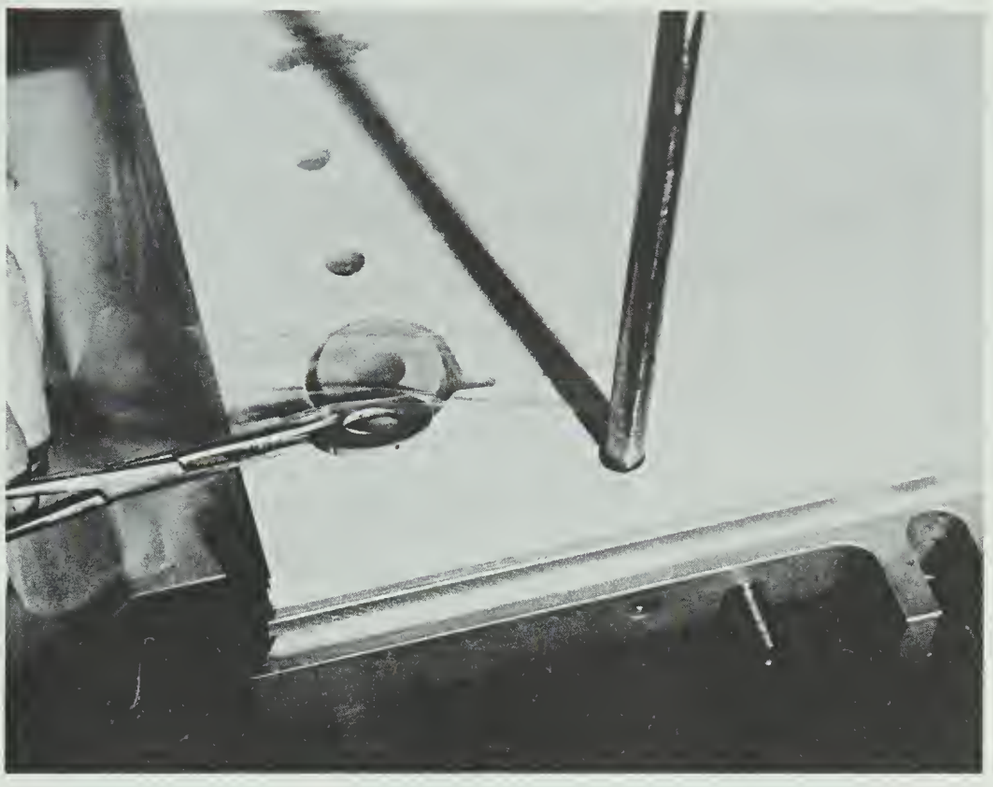

Figure 3. Shown is the insertion of a blood distribution disc between the double layered 0.5 mil teflon. Note the radially arranged openings.

corners, is inserted a disc with radially arranged openings (Figures 2 and 3). Blood passes up the column of discs, spreads radially through the discs between the double layers of teflon membrane and traverses the surface of the lung to exit at the diagonally opposite corner through similar discs.

On either side of the outer surface of the membrane, clear oxygen plugs are inserted in opposite corners to the blood distrubtion discs. Oxygen flows up the oxygen inlet column, through the oxygen plugs and traverses the surface of the lung to exit at the diagonally opposite corner via another clear oxygen plug and column. In this manner, oxygen lies outside the double layer of teflon with blood sandwiched between. Gas exchange occurs across the membranes.

Gas flow through the membrane lung consisted of 100% oxygen at a flow rate of 5 liters per minute and 2½-5 pounds per square inch pressure.

Bypass consisted of a femoral vein catheter (#10-16 Levin tube) threaded up the inferior vena cava to a point just above the diaphragm. Blood via this catheter was withdrawn by a Med. Sciences occlusive type roller pump at 30 cc./kg.flow/min and forced through the membrane oxygenator. Return from the oxygenator was through a bubble trap and heat exchanger, thence into the animal, via a #12-14 Bardic arterial cannula inserted into the femoral artery (Figure 4). 300 cc. of lactated Ringers solution was used to prime the circuit. Blood was maintained at normothermia through a heat exchanger and through the integral manifolding in the base and head of the membrane oxygenator. The membrane area consisted of 1 square meter per 10 kg.of body weight.

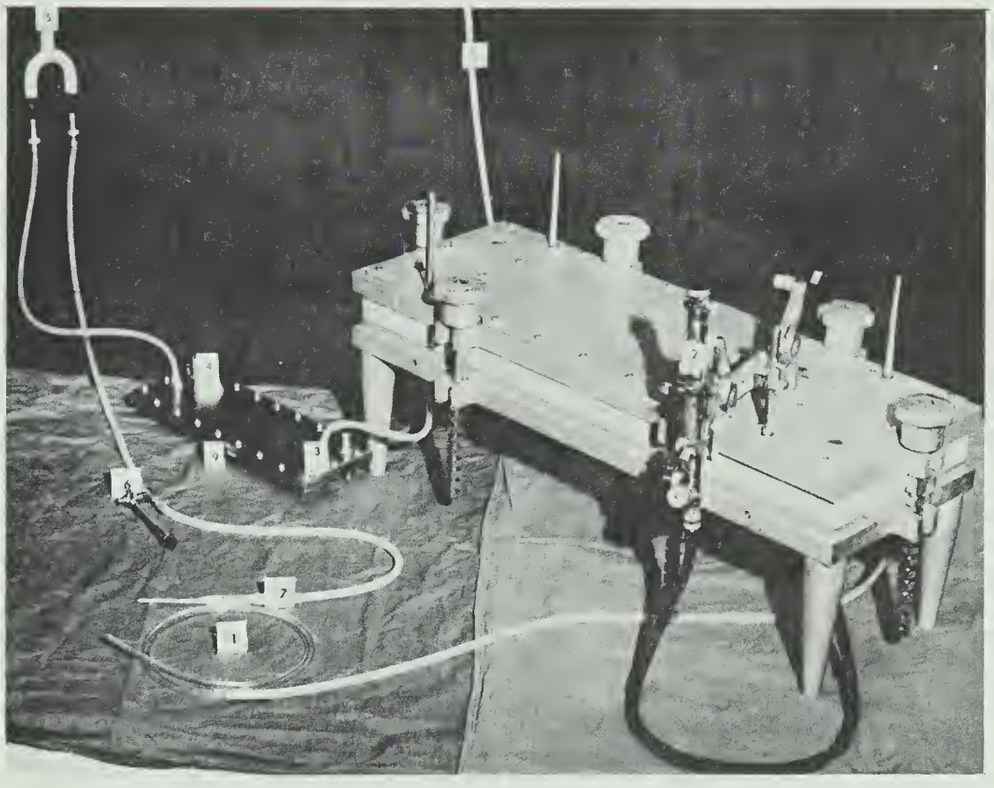

Figure 4. Shown is the Completely Assembled Membrane Lung of Peirce.

1) Levin tube from inferior vena cava, leads to inlet port of oxygenator.
2) Oxygen outlet flow regulator.
3) Oxygenator blood outlet.
4) Blood outlet of heat exchanger.
5) Bubble trap.
6) Dye injection valve used in subsequent studies.
7) Bardic arterial cannula for return to animal.
8) Oxygen inlet line.

Not shown is the Med Sciences pump which is inserted between 1 and the oxygenator.

Five animals were placed on partial bypass at a point at which the pO_2 value was numerically lower than the pCO_2 value. Six animals were placed on bypass at the time of airway restriction, that is, one hour after anesthesia. Those animals on prolonged perfusion requiring further anesthesia were given sodium pentobarbital in maximum doses of 3.8 mg. total at any one time to maintain the animals at a light level and blood gases were performed to the cessation of breathing.

C. Pump-Oxygenator Blood Distribution Studies

1. Cerebral perfusion pO_2 responses. Twenty mongrel dogs weighing 10 to 20 kg. were used in this study. Anesthesia consisted of sodium pentobarbital given intravenously at 30 mg./kg. body weight. Those animals requiring further anesthesia were given sodium pentobarbital in maximum doses of 3.8 mg. total at any one time to maintain the animals at a light level. A cuffed endotracheal tube was inserted. The left femoral artery was cannulated for following blood pO_2, pCO_2 and pH. These were performed on a Radiometer Copenhagen gas analyzer. After an initial withdrawal of 10 cc. blood, a second sample of 4 cc. was used for the gas determinations. All blood was then reinfused. Heparinization consisted of 3 mg./kg. body weight initially and 1 mg./kg. hourly thereafter.

All animals had #14-18 Levin tubes threaded up the right femoral vein and inferior vena cava to a level just above the diaphragm. Blood via this catheter was withdrawn from the animal by a Med. Sciences occlusive type roller pump at 30 cc./kg. to a Travenol pediatric bubble oxygenator. A bubble oxygenator was used in this group of experiments as it afforded far greater pO_2 supply to the tissues and it was hoped

a more definite cerebral tissue pO_2 response could be produced making comparison of the various bypass techniques easier. Approximately 400 cc. lactated Ringers solution was used to prime the circuit. A heating lamp directed toward the surface of the oxygenator bag served to maintain the animals temperature. A second Med. Sciences occlusive type roller pump served to return oxygenated blood to the animals.

Return was through a #10-14 Bardic arterial cannula inserted either into the femoral artery, in one group of five animals, into the aortic root via a catheter threaded up the femoral artery in another group, through the right axillary artery in another, and finally, into the left external jugular vein in the fourth group.

Once all surgical procedures were finished a control blood-gas determination was obtained. At the same time, cerebral tissue oxygen tensions were measured with the Beckman 160 gas analyzer and polarographic microelectrode. The Beckman 160 gas analyzer was previously calibrated with an oxygen-free sample, produced by means of bubbling pure nitrogen into saline, and with a known oxygen sample. The oxygen concentrations of the calibrating fluids were determined on a Radiometer Copenhagen gas analyzer.

Calibration of the Radiometer Copenhagen gas analyzer pCO_2 electrode was performed with gases of known CO_2% concentration (3.883% and 8.87%). Following barometric pressure and temperature corrections, the CO_2 range on the gas analyzer was set by passing these gases through the pCO_2 electrode.

The O_2 electrode was calibrated by passing through it nitrogen, which established a zero setting, and room air, the oxygen concentration of which was corrected for barometric pressure and temperature.

The pH electrode was calibrated with buffers of known concentration (pH 6.84 and pH 7.88).

The polarographic microelectrode (Figure 5) consists of a platinum-wire cathode, sealed in glass with only the tip exposed, surrounded by a silver tube anode. The tip of the electrode is covered by a fine polyethylene membrane, and the membrane and positive and negative poles of the electrode are bathed in an electrolyte solution. A constant polarizing current of 0.68 v. from the amplifier is applied to the platinum cathode. Oxygen molecules flow through the membrane and are reduced at the cathode. Reduction of oxygen molecules creates a flow of current which is proportional to the oxygen tension (pO_2) of the sample.

The electrode was positioned within the left cerebral hemisphere through a #18 gauge Riley needle, which in turn was passed through a predrilled hole affording a snug fit. This in turn allowed for no movement of the electrode. The site of penetration was 1 cm. to the left of the sagital suture and approximately 2 cm. posterior to the superior orbital ridge. The electrode was inserted to a depth of ½ -1 cm. following skull penetration and allowed to stabilize (Figures 6 and 7).

The airway was then restricted by a #14 needle inserted into the endotracheal tube. No I.V. fluids, bicarbonate or medications were given to the animals. Further blood-gas sampling was done every ten

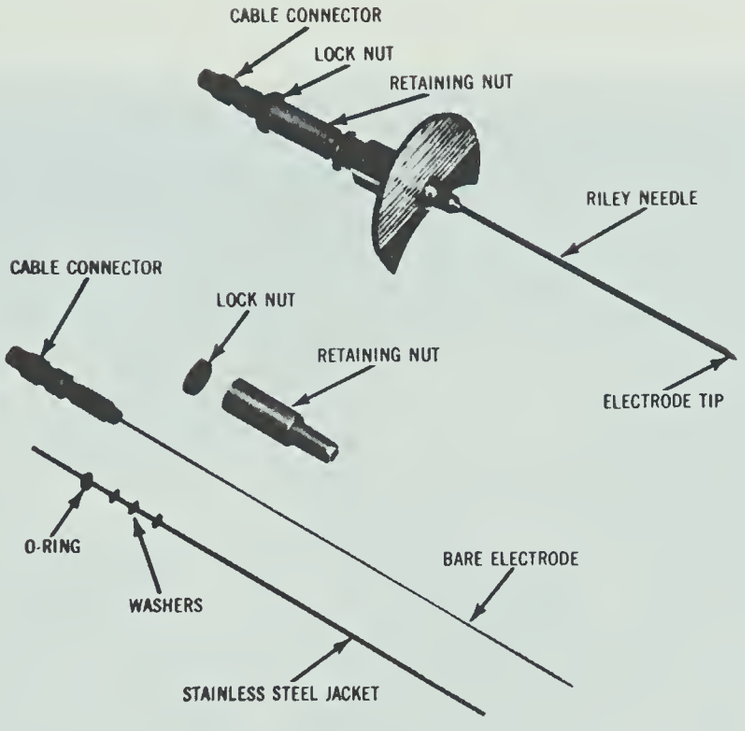

Figure 5. Parts of the Oxygen Microelectrode.

Figure 6. Apparatus for Measuring Intracerebral Oxygen Tension during Perfusion.
1) Bypass return line to axillary artery.
2) Venous drainage line from inferior vena cava.
3) Oxygen microelectrode.
4) Endotracheal tube with #14 needle.
Gas analyzer in left background.

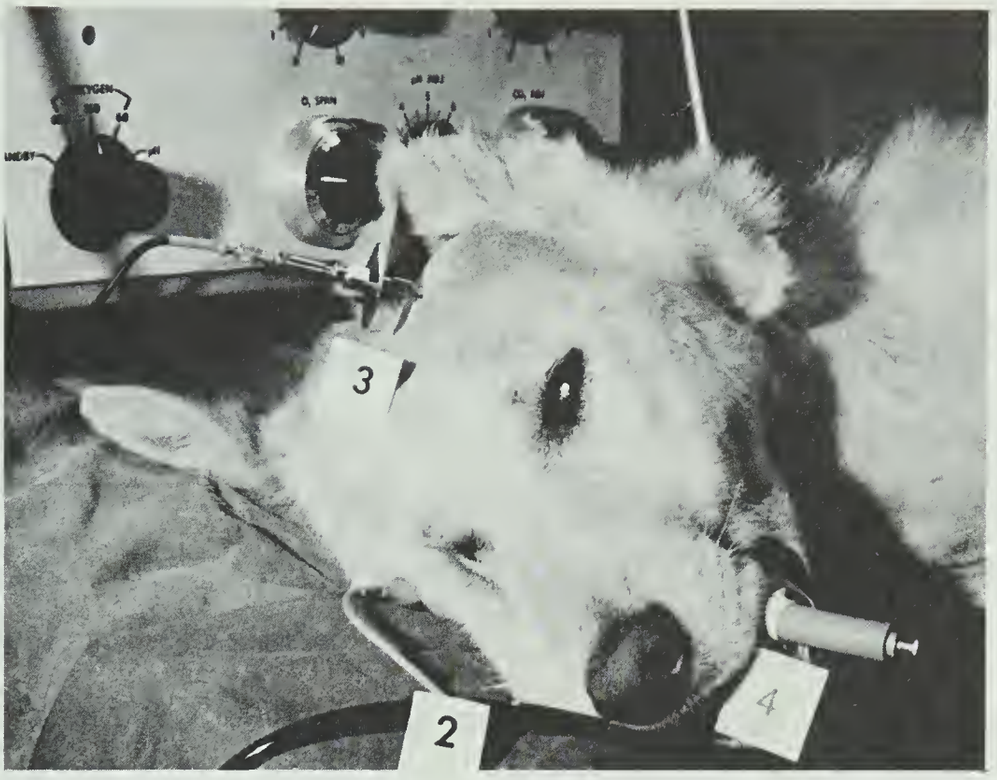

Figure 7. Closeup of Main Features of Figure 6.

2) Venous drainage line.
3) Oxygen microelectrode.
4) Endotracheal tube with #14 needle.

minutes, the gas analysis being done immediately upon withdrawal. Cerebral tissue pO_2 readings were taken every 15 minutes. If the animals were not distressed, the period between blood-gas samples was gradually increased. At a point when the animals' blood-gas pO_2 readings were less numerically than the blood gas pCO_2, partial cardiopulmonary bypass was instituted. Partial cardiopulmonary assist was carried out for 1½-2 hours. Blood-gases and cerebral tissue pO_2's were monitored to the end of the cardiopulmonary assist.

2. Pump-oxygenator and cardiac dye distribution studies. Twenty mongrel dogs weighing 8.5 to 29 kg. were used in this study. Following intravenous anesthesia of 30 mg%/kg. body weight sodium pentobarbital, all animals received cuffed endotracheal tubes which had been previously tested for leaks. Those leaking were replaced at once. Any animals requiring further anesthesia were given sodium pentobarbital in maximum doses of 3.8 mg. total at any one time to maintain the animals at a light level.

Following shaving of the groins, neck and axilla, all animals were placed in the supine position on the operating table. Fore and hind limbs were secured in the outstretched position.

A one inch-incision was made in the left axilla just overlaying the insertion of the pectoralis major muscle. The muscle fibers were split. Exposure was enhanced by inserting one finger from each hand into the split muscle and stretching the tissues. This facilitated the approach to the axillary vessels. The left axillary artery was cannulated with a #PE 160 polyethelene catheter which served to

follow the animals systemic blood pressure. In those cases requiring an axillary artery return for the bypass, the right axillary artery was similarly exposed and cannulated with a #10-12 Bardic arterial cannula.

In both groins, skin incisions were made paralleling the course of the femoral vessels. Blunt dissection exposed the femoral vein and artery on both sides. The four vessels were encircled with ties. A Levin tube varying in size from #12-18 French was inserted into the right femoral vein and threaded up to approximately the diaphragmatic level. This was tied loosely to allow some manipulation once the animals were placed on partial bypass should drainage prove insufficient. Blood via this tube was then lead through a Med. Sciences occlusive type roller pump to the inlet port of the membrane oxygenator (Figure 4).

The right femoral artery, in the case of a femoral artery return type of bypass, was cannulated with a #10-16 Bardic arterial cannula. In the case of an aortic root return, a #10-14 Levin tube was threaded up the right femoral artery until resistance was encountered. This was usually at the level of the aortic valve. In most cases, the catheter could be advanced a little further and presumably doubled upon itself, for when the clamp was removed from the catheter, flow was absent. The catheter was then slowly withdrawn and, usually with unkinking, strong arterial pulsation and flow would occur. This was then securely tied in place.

The left femoral artery was tied leaving approximately 2 cm. on either side of the tie. Bardic arterial cannulae of size #12-14

were inserted on either side of the tie, one facing, on the proximal side of the tie, upstream, and the one on the distal side, facing downstream. Between these 20 inches of 3/8 inside diameter silastic tubing was inserted. The tubing was divided in the middle, which allowed the insertion of a 4 mm. Zepeda flowmeter. Distal to the flowmeter, a stainless steel fitting was used which allowed sampling of blood after it had passed through the flowmeter. Into this fitting was inserted a #PE 280 tubing of 48- inch length, which served for blood gas samples and for dye dilution curves (Figure 8). When the femoral artery was not used for bypass return, i.e., veno-venous bypass and axillary artery return, the right and left femoral arteries were cannulated as for the left and the two proximal limbs connected via a Y-shaped connector. A single branch then ran to the flowmeter following which another Y-shaped connector split the stream and returned them once more to their respective sides (Figures 9 and 10). When the flowmeter was required elsewhere, a stainless steel connector was inserted in its place. A syringe could be attached to this connector which would allow the extraction of any remaining air prior to resuming flow through this area.

In the midline of the neck, a two-inch skin incision was made. Through this, with blunt dissection, one could expose and retrieve both carotid arteries and both external jugular veins. In all cases the right jugular vein was catheterized with a #PE 200 polyethelene tube of 24-inch length. This was advanced until right ventricular pressure readings were obtained. This was then tied in place. This served for right ventricular pressure tracings during respiratory

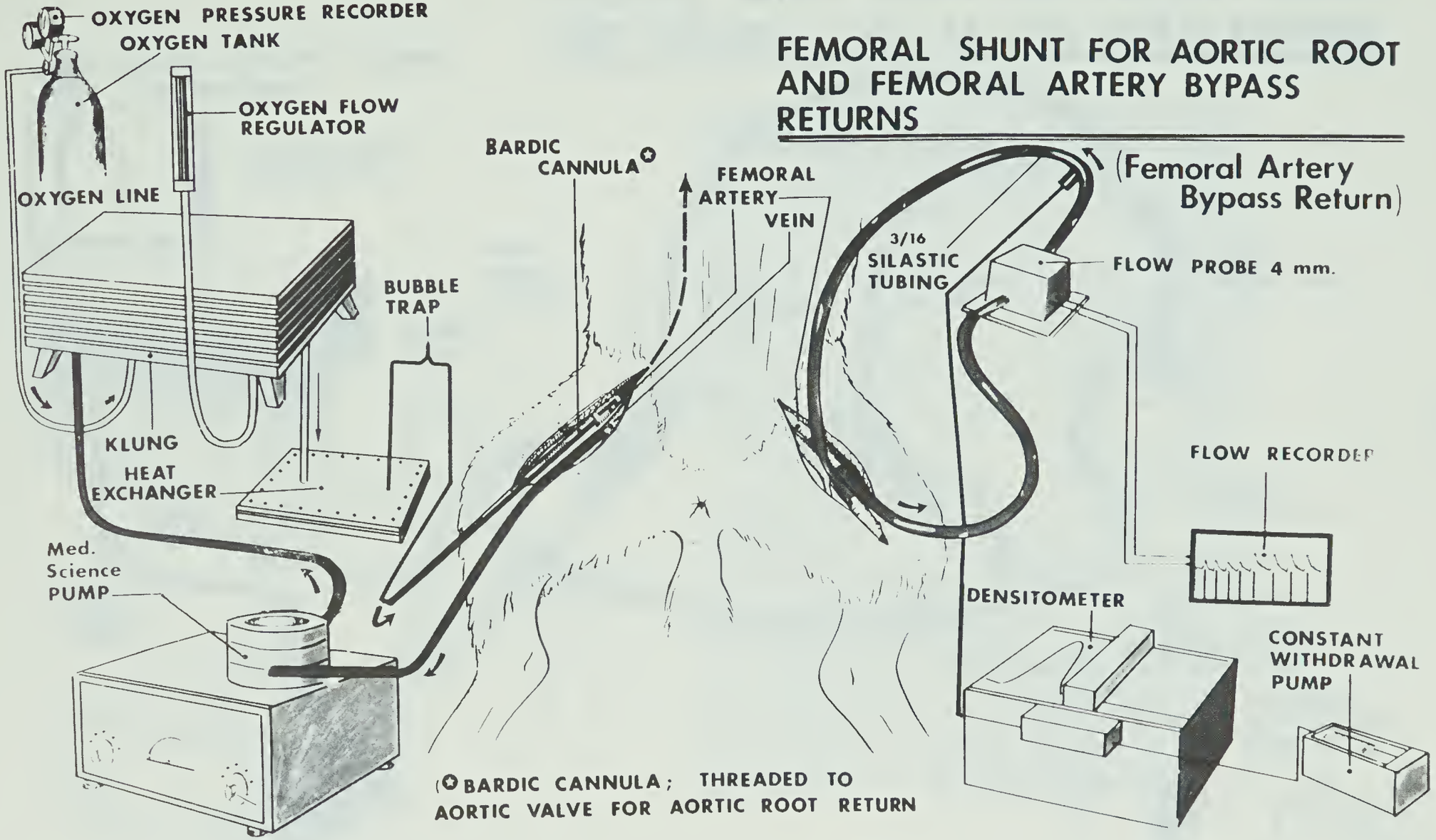
FEMORAL SHUNT FOR AORTIC ROOT AND FEMORAL ARTERY BYPASS RETURNS
OXYGEN PRESSURE RECORDER
OXYGEN TANK
OXYGEN FLOW REGULATOR
OXYGEN LINE
BUBBLE TRAP
KLUNG
HEAT EXCHANGER
Med. Science PUMP
BARDIC CANNULA
FEMORAL ARTERY
VEIN
(Femoral Artery Bypass Return)
3/16 SILASTIC TUBING
FLOW PROBE 4 mm.
FLOW RECORDER
DENSITOMETER
CONSTANT WITHDRAWAL PUMP
(BARDIC CANNULA; THREADED TO AORTIC VALVE FOR AORTIC ROOT RETURN

Figure 8.

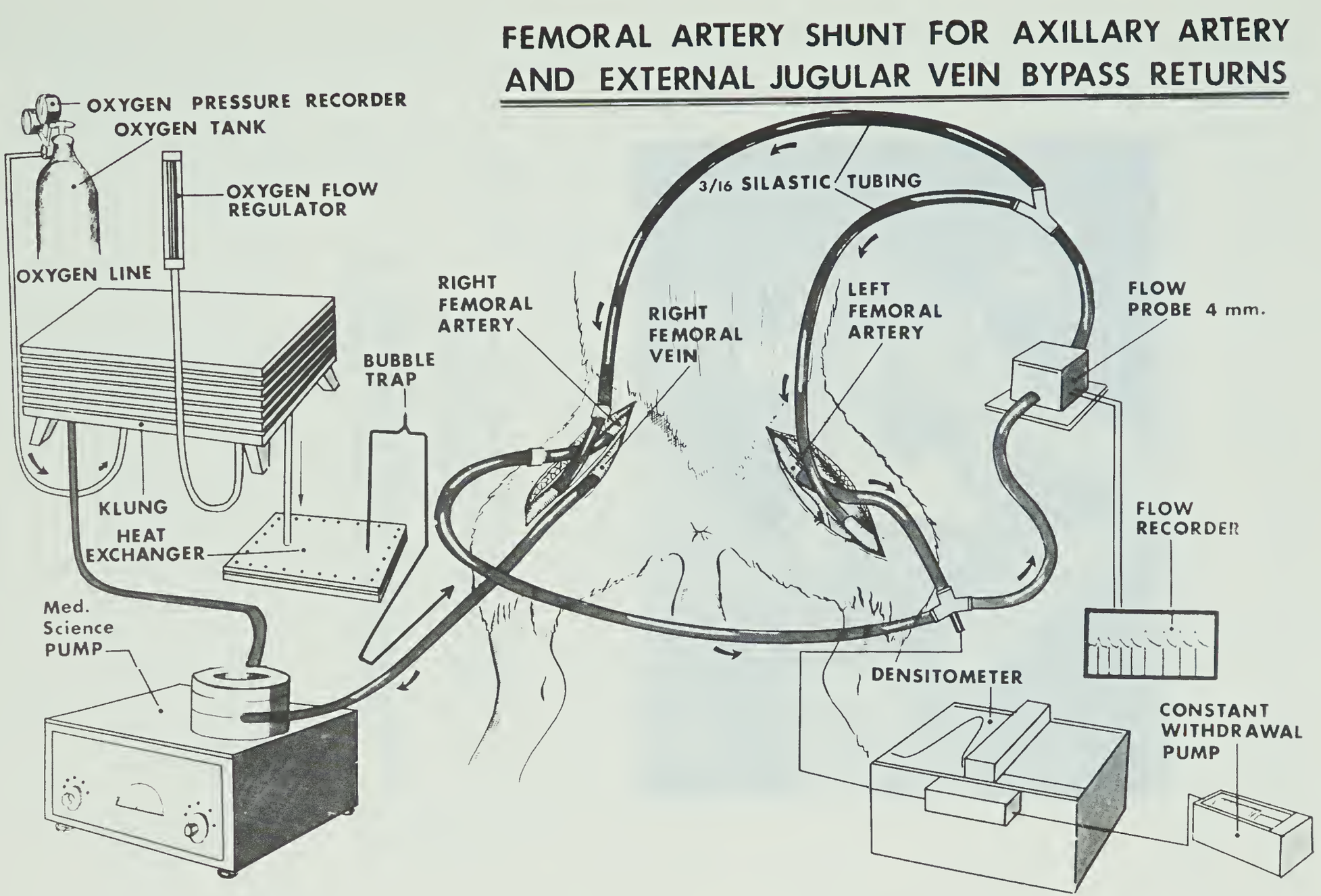
FEMORAL ARTERY SHUNT FOR AXILLARY ARTERY AND EXTERNAL JUGULAR VEIN BYPASS RETURNS
OXYGEN PRESSURE RECORDER
OXYGEN TANK
OXYGEN FLOW REGULATOR
OXYGEN LINE
KLUNG
HEAT EXCHANGER
BUBBLE TRAP
Med. Science PUMP
3/16 SILASTIC TUBING
RIGHT FEMORAL ARTERY
RIGHT FEMORAL VEIN
LEFT FEMORAL ARTERY
FLOW PROBE 4 mm.
FLOW RECORDER
DENSITOMETER
CONSTANT WITHDRAWAL PUMP

Figure 9.

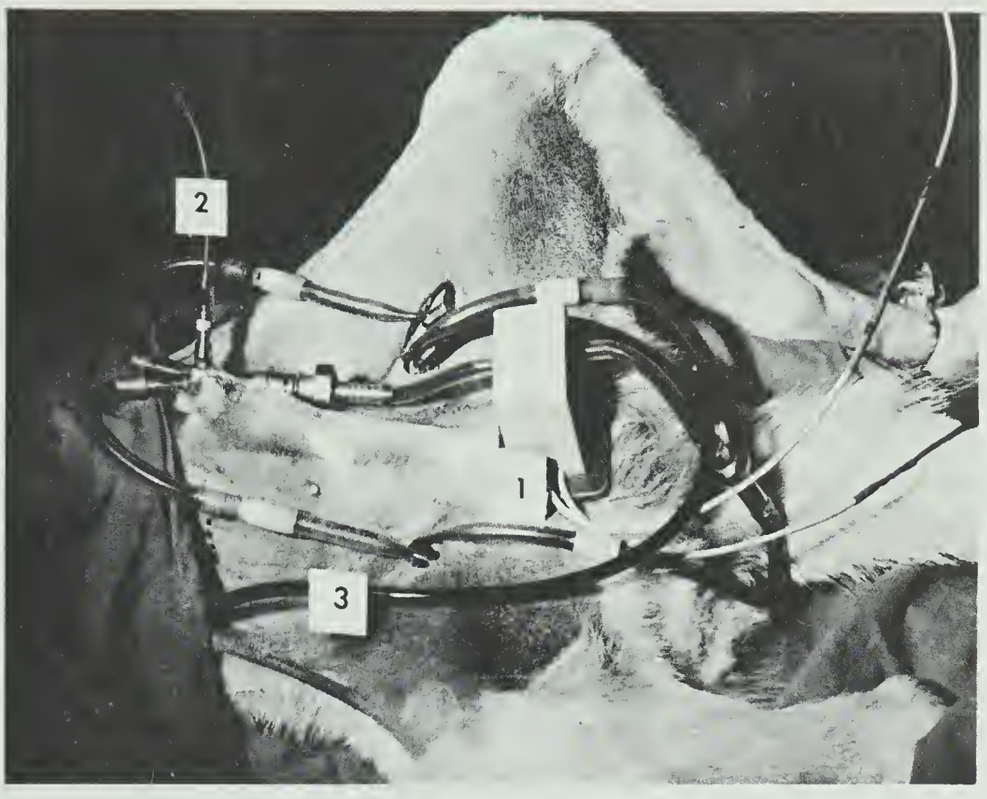

Figure 10. Femoral Artery Shunt for Axillary Artery and External Jugular Vein Bypass Returns.

1) Flow meter block.
2) Blood sample line to cardiodensitometer.
3) Venous drainage line to oxygenator.

distress and partial cardiopulmonary bypass and for injecting Cardio-green dye into the right ventricle.

The left external jugular vein was catheterized with a #16 Bardic arterial cannula, in those cases on veno-veno bypass, and served as a site for re-entry of freshly pump-oxygenated blood.

Both carotid arteries were retracted from the depths of the neck and tied. On the proximal side of the tie, #14 Bardic arterial cannulae were inserted. These were joined with 10-inch lengths of $^{3}/8$ inside diameter silastic tubing inserted into a stainless steel Y-shaped connector of larger size than the tubes. This then led by means of a single short length (two inches) of tubing to a 4 mm. Zepeda flowmeter. Exiting from the flowmeter, the blood once again went through a Y-connector and diverged to return via two #12 Bardic arterial cannulae inserted in the carotid arteries distal to the tie. Provision was also made in the connector for inserting a blood-gas sample line and for a catheter as previously described for dye-dilution curve recording (Figures 11 and 12). The catheter, #PE 280 polyethelene tubing of 48-inch length, was then fed to a Beckman cardiodensitometer. A Harvard constant withdrawal pump served to draw the sample through the densitometer at a rate of 46 cc./min.

Dye Preparation. Densitometer calibration was performed by adding 10 ml. of aqueous solvent to standard 50 mg. vials of Cardio-green dye*

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* A product of Hynson, Westcott and Dunning, Inc., Baltimore, Maryland, U.S.A.

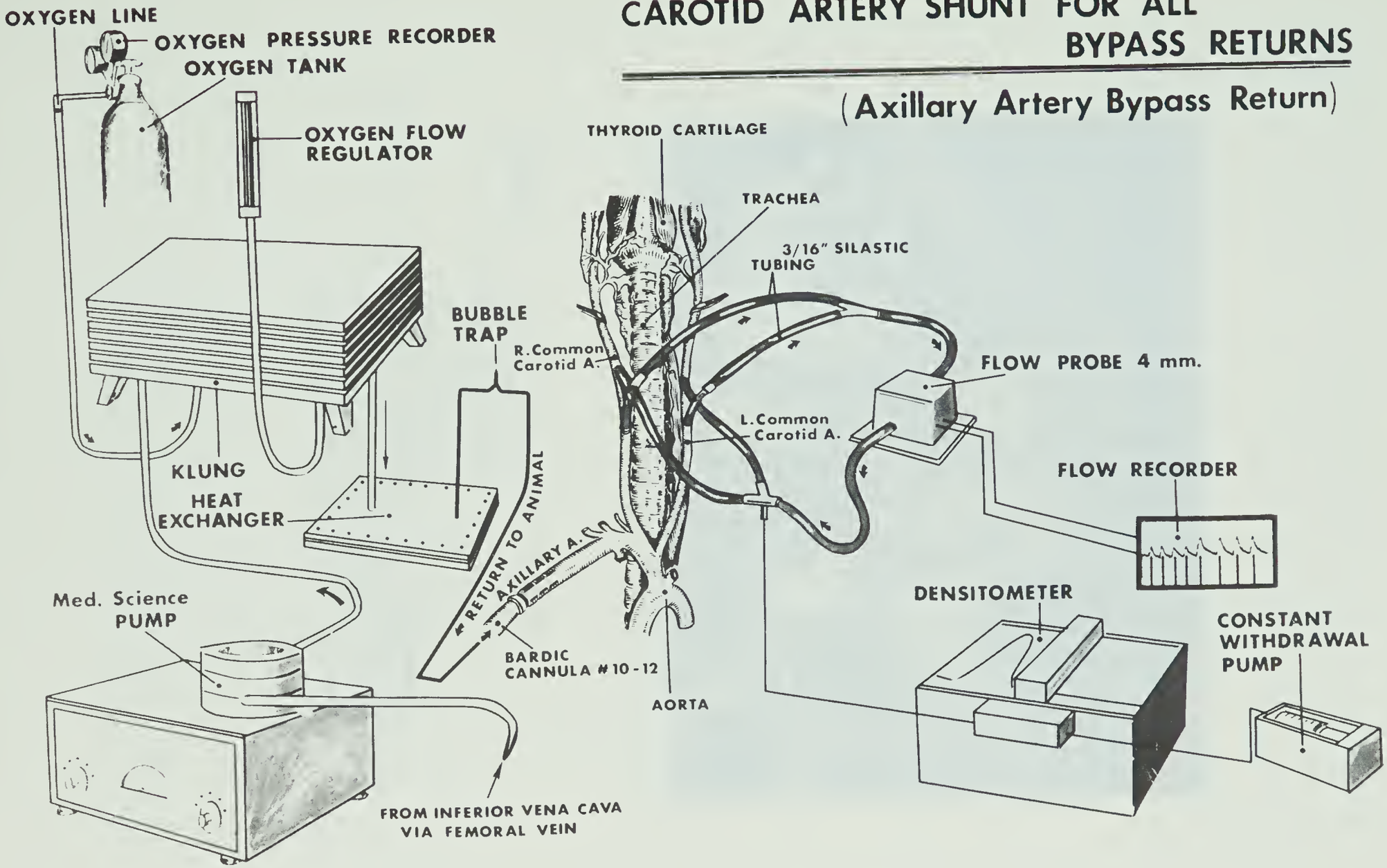
CAROTID ARTERY SHUNT FOR ALL BYPASS RETURNS
(Axillary Artery Bypass Return)
OXYGEN LINE
OXYGEN PRESSURE RECORDER
OXYGEN TANK
OXYGEN FLOW REGULATOR
THYROID CARTILAGE
TRACHEA
3/16" SILASTIC TUBING
BUBBLE TRAP
R.Common Carotid A.
FLOW PROBE 4 mm.
L.Common Carotid A.
FLOW RECORDER
KLUNG
HEAT EXCHANGER
RETURN TO ANIMAL
AXILLARY A.
Med. Science PUMP
DENSITOMETER
CONSTANT WITHDRAWAL PUMP
BARDIC CANNULA #10-12
AORTA
FROM INFERIOR VENA CAVA VIA FEMORAL VEIN

Figure 11.

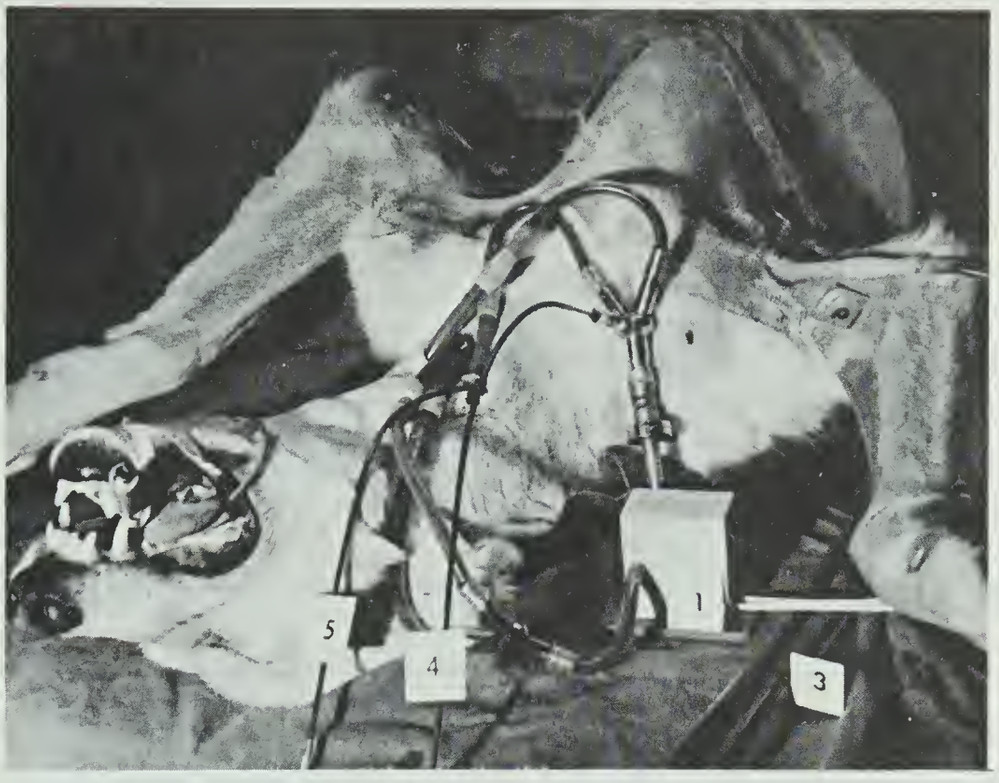

Figure 12. Carotid Artery Shunt for all Bypass Returns.

1) Flow meter block.
2) Axillary artery return line from oxygenator.
3) Venous drainage line to oxygenator.
4) Blood sample line to cardiodensitometer.
5) Right ventricular catheter for dye injections and ventricular pressures.

(Indocyanine green dye). Several dilutions of this were performed yielding concentrations of the dye in the solvent of 24.0, 12.0, 2.0 and 3.0 mg. per liter. These concentrations were then passed through a Beckman densitometer and calibration curves were constructed from the deflections noted. The deflections obtained during experimental conditions could then be compared to the calibration curves if quantitation was required.

Dye injections into the animals were given in the form of a concentrated fluid placed in the right ventricular catheter and flushed with saline at the rate of 120 cc./min. Prior to dye injection withdrawal of blood for dilution curves was commenced. The volume of dye injected was on a ml./body weight basis (see below).

Weight (kg.)	Dye Conc. (mg.)	Dye Vol. (cc.)
5 - 15	2.0	0.4
15 - 25	2.5	0.5
25 - 35	5.0	1.0

Flow Probe Calibrations. The circuit consisted of a reservoir in a water bath for maintenance of temperature at 37°C. Blood was drawn from the reservoir by means of a Med. Sciences occlusive type roller pump and pumped through a 4 mm. Zepeda flowprobe, which was in turn connected to a Zepeda electromagnetic flowmeter driver EPD-2RD, incorporated in a Beckman Offner recorder. From the flowmeter the blood ran into a graduated cylinder. For flows under 200 cc./min.,

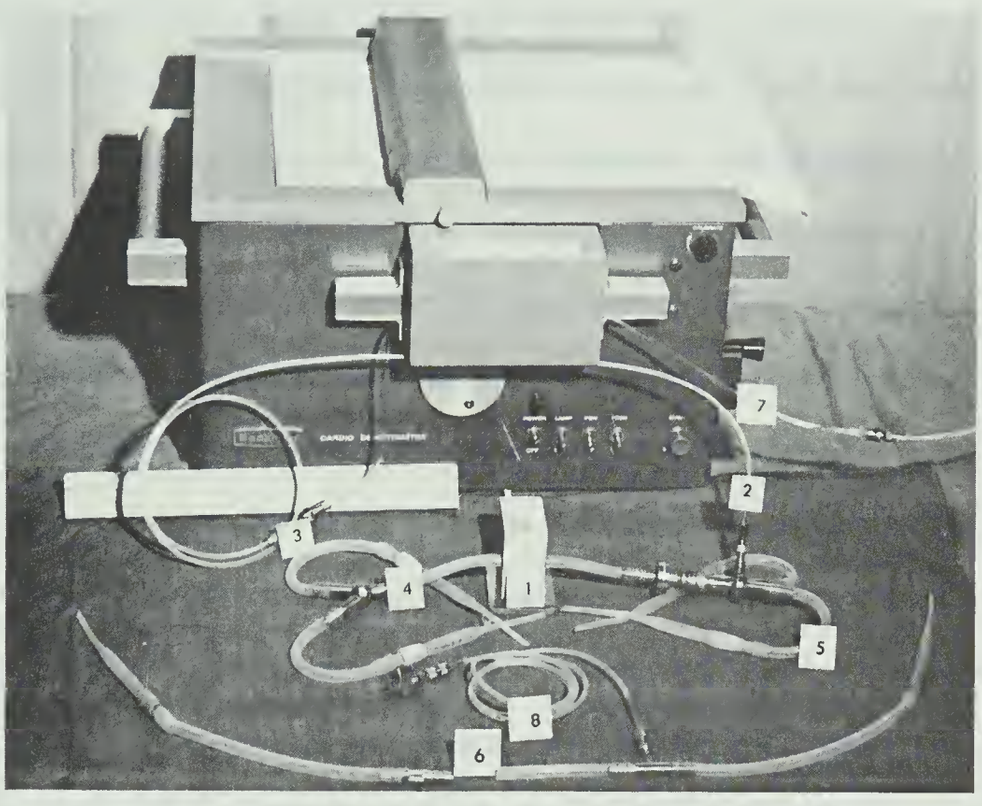

Figure 13. Apparatus for Dye Distribution Investigations.

1) Flow meter block and carotid artery shunt.
2) Cardiodensitometer line distal to flow meter.
3) Blood sample line to cardiodensitometer.
4) Proximal limb of shunt.
5) Distal limb of shunt.
6) Unilateral femoral artery shunt - flow meter inserts here (for aortic root and femoral artery bypass returns).
7) Cardiodensitometer line to Harvard constant withdrawal pump.
8) Blood sample line - inserts into cardiodensitometer. Beckman Cardiodensitometer in background.

flows were measured in the cylinder for a period of a minute; for flows over 200 cc./min., measurement was carried out for only half a minute. Mechanical and electrical zeros were established as outlined in the Zepeda manual.

Whole blood was centrifuged and the plasma separated to give a hematocrit of 64. Varying flow rates were measured and recorded with an amplifier setting of 0.2 in all cases, and pre-amplifier settings of 0.5, 1.0, 2.0 and 5.0. Plasma was then added to the blood giving a new hematocrit of 47 and the process repeated. A final concentration was made producing a hematocrit of 31 and again a number of flows were measured and recorded at different pre-amplifier settings. The results were then plotted as blood flow in cc./min. vs. microvolt deflection (Figure 26).

General. Following the surgical preparation of all dogs, a blood-gas sample was taken and the airway restricted by means of a #14 needle inserted into the endotracheal tube. Blood-gas determinations were done immediately upon withdrawal on a Radiometer Copenhagen gas analyzer. After an initial withdrawal of 10 cc. blood, a second sample of 4 cc. was used for the blood-gas determination. All blood was then returned to the animal. Further blood-gas sampling was carried out every ten minutes and, unless distressed, the period between blood-gas samples was gradually increased.

Partial cardiopulmonary assist with the membrane oxygenator of Peirce was instituted at a point when the pO_2 readings fell below the pCO_2 readings. The twenty animals were placed into four groups of five and consisted, as in the cerebral tissue pO_2 studies, of a

femoral artery return group, an aortic root return group, a right axillary artery return group and a veno-veno bypass group with a left external jugular vein return.

Partial cardiopulmonary assist (30 cc. flow/kg. body weight) was carried out for one-half hour, at which point dye dilution curves were performed. Dye concentrations and methods of injection were previously outlined. Prior to injection of Cardio-green dye blood flow was recorded, and if stable, withdrawal of blood for the curve was begun. Once a stable baseline for the dye curve was established the injection took place. Blood flow was monitored before, during and immediately after the curve.

After recording dye curves and blood flow at a particular level, either femoral or carotid arteries, the flowmeter probe was removed from the shunt line and replaced by a straight-through stainless steel connector. The flowmeter probe was then inserted in the shunt at the level not yet recorded. Once inserted and while the previous blood sample was being returned to the animal, the flow probe was once again calibrated. The switch over and calibration or zero check usually required approximately three minutes before the next dye injection.

Once dye dilution curves and flows had been obtained from both carotid and femoral sites after one-half hour of partial bypass, the procedure was terminated.

Dye dilution recordings obtained at both carotid and femoral artery levels include those obtained by right ventricular injection and return line injection at a point 18 inches prior to re-entry

into the animal. Right ventricular injection allowed observation of the distribution of that part of the total blood flow contributed by the cardiac output while under partial cardiopulmonary bypass. Pump oxygenator line injection allowed observation of blood distribution contributed by the pump-oxygenator system. Changes in the contribution of one component should be reflected by changes in the other. That is, a lesser contribution of the cardiac output down the aorta should be reflected in a greater contribution from the pump-oxygenator system. A femoral artery return type of bypass would be expected to show a greater contribution by the pump-oxygenator system at the femoral artery level than that contributed by the heart.

CHAPTER III

RESULTS AND DISCUSSION

The dynamic processes of ventilation, diffusion and perfusion have as their function the maintenance of normal pressures of O_2 and CO_2 in the alveolar gas and pulmonary capillary blood, i.e., the arterialization of the venous blood. Examination of the arterial blood for its O_2 and CO_2 pressure and content will show how adequately the lung is accomplishing its primary purpose.

1. Arterial Blood Oxygen. Blood combines with O_2 in two ways:

(a) In physical solution in the watery parts of the blood as dissolved O_2.

(b) In chemical combination with hemoglobin as HbO_2.

In each case the amount of O_2 taken up depends on the pO_2 to which the plasma or blood is exposed. In the case of Hb, the amount of O_2 associated is not linearly related to the pO_2, as it is in the case of dissolved O_2.

A graph of O_2 content (or percent of saturation) against pO_2 is not a straight line but an S-shaped curve which has a very steep slope (between 10 and 50 mm. Hg. pO_2) and a very flat portion (between 70 and 100 mm. Hg. pO_2). The unusual shape of this HbO_2 dissociation curve is a distinct advantage for several reasons:

(a) If arterial pO_2 decreases from 100 to 80 mm. Hg. as a result of cardiopulmonary disease, the Hb of arterial blood will still be almost maximally saturated (94.5%) and the tissues will not suffer from anoxia.

(b) When arterial blood passes into tissue capillaries and is exposed to the tissue tension of O_2 (about 40 mm. Hg.), Hb gives up

large quantities of O_2 for utilization by the tissues.

Hypoxia or hypoxemia refers specifically to a decrease in the amount of O_2 in arterial blood and may be brought about by many conditions (Table I). Any type of alveolar hypoventilation, whether due to central respiratory depression or neuromuscular disorder in a patient with normal lungs or due to airway obstruction or rigid lungs or pleura, must of course result in lower alveolar pO_2, decrease in arterial pO_2 and decrease in arterial O_2 saturation.

When there is uneven distribution of alveolar gas and blood there must be a decrease in arterial blood pO_2 relative to mean alveolar pO_2. Unless total alveolar ventilation is increased, this must result in arterial hypoxemia. However, total alveolar ventilation may be increased enough so that even previously poorly ventilated regions of the lungs may receive enough O_2 to arterialize the blood flowing through alveolar capillaries.

When there is impairment of diffusion, arterial pO_2 must be low relative to alveolar pO_2 but the difference may be insignificant in the resting state. In the great majority of cases with a significant decrease in pulmonary diffusing capacity for CO, there is still a normal arterial O_2 saturation. In many cases, this may be achieved by the hyperventilation characteristics of this disorder.

Intrapulmonary venous-to-arterial shunts represent a special type of uneven ventilation in relation to blood flow. Because some mixed venous blood bypasses ventilated alveoli, both the pO_2 and the saturation of arterial blood must be reduced below normal.

TABLE I: CAUSES OF HYPOXIA

	(↑ = increase; ⇄ = no change; ↓ = decreased) EFFECT ON ARTERIAL BLOOD			
	O_2 Tension	O_2 Content	O_2 Saturation	CO_2 Tension
1. Normal lungs but inadequate oxygenation				
(a) Deficiency of O_2 in atmosphere (decreased ambient pressure; addition of other gases to air)	↓	↓	↓	↓
(b) Hypoventilation (neuromuscular disorders)	↓	↓	↓	↑
2. Pulmonary disease				
(a) Hypoventilation due to airway or pulmonary disease	↓	↓	↓	↑
(b) Uneven distribution of alveolar gas and/or pul. capillary blood flow	↓*	↓*	↓*	↓, ⇄ or ↑
(c) Impairment of diffusion	↓	↓	↓	↓
3. Venous-to-arterial shunts (intrapulmonary or intracardiac)	↓	↓	↓	↓, ⇄ or ↑
4. Inadequate transport and delivery of O_2				
(a) Anemia; abnormal (inactive) Hb	⇄	↓	⇄†	⇄
(b) General circulatory deficiency	⇄	⇄	⇄	⇄
(c) Localized circulatory deficiency (peripheral, cerebral, coronary vessels)	⇄	⇄	⇄	⇄
5. Inadequate tissue oxygenation				
(a) Tissue edema	⇄	⇄	⇄	⇄
(b) Abnormal tissue demand	⇄	⇄	⇄	⇄
(c) Poisoning of cellular enzymes	⇄	⇄	⇄	⇄

* Unless the patient is hyperventilating.

† Saturation of active hemoglobin is normal.

2. Arterial Carbon Dioxide and pH. Unless CO_2 has been added to inspired gas, the CO_2 content of venous blood, alveolar gas and arterial blood originates in tissue metabolism. Carbon dioxide diffuses from tissue cells into capillary blood and is carried in chemical combination and in physical solution in the venous blood to the lungs, where a part of it diffuses into alveolar gas and is eliminated in the expired gas.

The processes involved in the loading and transport of CO_2 briefly are:

(a) Diffusion of CO_2 from Tissue Cells into Capillary Blood. - In actively metabolizing cells, tissue pCO_2 is greater than pCO_2 of arterial blood flowing through systemic capillaries. Carbon dioxide, therefore, diffuses from the cells into the plasma.

(b) Chemical Reactions in the Plasma. - (i) Some CO_2 dissolves in the plasma. A very small amount of this reacts slowly with water to form carbonic acid ($H_2O + CO_2 \rightleftarrows H_2CO_3$). This H_2CO_3 dissociates into $H^+ + HCO_3^-$ and the H^+ is buffered by plasma buffering systems.

(ii) Dissolved CO_2 in plasma reacts with the amino group of plasma proteins to form carbamino compounds.

(c) Chemical Reactions Within the Erythrocyte. - Most of the CO_2 that diffuses from tissue cells into the plasma passes into the erythrocytes. Intra-erythrocytic CO_2 reacts in three ways:

(i) Some remains within the red blood cell as dissolved CO_2.

(ii) Some combines with the NH_2 groups of Hb to form carbamino compounds.

$$R - NH_2 + CO_2 \rightleftarrows R - NHCOO^- + H^+$$

This is a very rapid chemical reaction which requires no special catalyst. The H^+ is buffered by portions of the Hb molecule. This process is facilitated by the simultaneous loss of O_2 from capillary blood to the tissues ($HbO_2 \rightleftarrows Hb + O_2$) because the conversion of oxyhemoglobin to reduced Hb causes Hb to become a weaker acid and to take up additional H^+ with little change in pH.

(iii) Some CO_2 combines with water to form H_2CO_3, which then dissociates to form H^+ and HCO_3^- ions. The conversion of CO_2 and H_2O into H_2CO_3 is a very rapid reaction only because of the presence of an enzyme, carbonic anhydrase. Carbonic anhydrase is concentrated within the erythrocyte, and this reaction (the hydration of CO_2) is an important and rapid one in blood only within the red blood cells.

This reaction results in the formation of H^+ ions which are also buffered by chemical groups of the Hb molecule with minimal change in pH; like the reaction in c (ii), this is aided by simultaneous conversion of some HbO_2 to Hb as O_2 passes into the tissues.

This reaction also results in the accumulation of a high level of HCO_3^- ions within the red blood cell. Bicarbonate ions then diffuse into the plasma to re-establish equilibrium of HCO_3^- between cells and plasma. If this diffusion of anions were accompanied by diffusion of an equal number of cations, electrical neutrality of the erythrocyte would be maintained. However, the red cell membrane is not freely permeable to cations and so anions from the plasma (Cl^-) diffuse into the erythrocyte (chloride shift) to achieve electrical neutrality. Some movement of water inward occurs simultaneously to maintain osmotic equilibrium; this results in a slight swelling of

erythrocytes in venous blood, relative to those in arterial blood.

The reverse of the foregoing reactions occurs in the pulmonary capillaries when O_2 is added and CO_2 unloaded.

Several points are of special interest:

1. Although plasma contains much more CO_2 (in all forms) than do the red blood cells (in all forms), and although the plasma transports more than 60% of CO_2 added to capillary blood, the chemical reactions within the red blood cell provide practically all of the additional bicarbonate ions transported in the plasma. If the enzyme carbonic anhydrase is completely inhibited, the reaction $CO_2 + H_2O \rightleftarrows H_2CO_3$ proceeds slowly and is not complete in the systemic capillary or even in the time that the blood flows through the vein en route to the heart. The reverse reaction, $H_2CO_3 \rightleftarrows CO_2 + H_2O$, which normally occurs during the time that venous blood is in the pulmonary capillaries, is also slow in the absence of carbonic anhydrase and continues long after the blood has left the pulmonary capillaries and entered the systemic circulation.

2. Carbon dioxide loading and O_2 unloading in body tissue capillaries are mutually helpful; an increase in capillary blood pCO_2 (and decrease in pH) facilitates the unloading of O_2 (the Bohr effect), and the unloading of O_2 (change from HbO_2 to Hb) facilitates the loading of CO_2 (the Haldane effect).

3. Just as the amount of O_2 carried by the blood is related to the pO_2 to which blood is exposed, so the amount of CO_2 in blood is related to the pCO_2 of the blood. In the physiologic range of CO_2 content and tension, the relationship between the two is almost linear,

whereas the O_2 dissociation curve is S-shaped.

Increases in arterial blood pCO_2 mean either that the whole lung or a major portion of it is hypoventilated. Arterial pCO_2 is never increased by pure impairment of diffusion. It may be increased slightly by a venous-to-arterial shunt, though as a rule, hyperventilation reduces the pCO_2 in the alveolar capillary blood sufficiently to compensate for the higher pCO_2 in shunted blood. When there is uneven distribution of gas in relation to blood, arterial pCO_2 will rise if alveolar ventilation is decreased or normal; it will also rise if total alveolar ventilation is increased if the major portion of the alveolar ventilation is going to regions with little pulmonary capillary blood flow.

When there is pulmonary insufficiency of CO_2 exchange, there must also be pulmonary insufficiency of O_2 exchange, unless high concentrations of O_2 are breathed.

3. Defences Against pH Change. The arterial pCO_2 is exquisitely responsive to changes in ventilation. Sudden retention of CO_2 anywhere in the body will, by increasing the pCO_2, immediately lower the local pH; in addition, if CO_2 continues to accumulate in one body compartment, it will soon diffuse to other compartments and lower their pH.

The lungs are the most important organ in the body for acid excretion. Whenever arterial pCO_2 tends to rise, the medullary respiratory centre is stimulated. Alveolar ventilation is increased and the pCO_2 returns to normal. This delicate mechanism operates only

when the sensitivity of the respiratory system is normal, the nervous connections between the centre and the respiratory muscles are intact, the respiratory muscles are normal and the lung is not seriously diseased.

(a) Chemical Buffering. - Hemoglobin minimizes the pH change in the blood by its remarkable oxygen-dependent buffering action against carbonic acid. Plasma and intracellular proteins are generally less effective buffers; buffering action in the extracellular and cerebrospinal fluids, because they are poor in protein, is much more dependent on the bicarbonate level.

(b) Tissue Buffering. - In addition to chemical buffer action, time-dependent migrations of H^+ and HCO_3^- ions also act to minimize pH changes in respiratory acidosis. Hydrogen ions enter cells by some exchange mechanism involving potassium: K^+ moves out of cells, and serum potassium rises in experimental respiratory acidosis.

(c) The Renal Defence. - The slower mechanisms of defence against pH change operate in the kidney: H^+ is directly excreted and HCO_3^- reabsorbed. An elevated pCO_2 is probably the stimulus for bicarbonate reabsorption during acute respiratory acidosis. Hydrogen ion excretion is speeded up and the titratable acidity and NH_4Cl concentration of the urine are increased. This renal compensation requires three to five days and is rarely complete.

A. The Establishment of a Time of Cardiopulmonary Bypass Assist

The series of control animals is presented in Figures 14 to 16 which illustrate the blood-gas picture from airway restriction to

death. Our prime concern was the pattern presented by the pO_2 and pCO_2 rather than the pH, although the latter is plotted to make the picture complete.

From the time of airway restriction, one notes the catastrophic fall in pO_2 in some animals (Figure 14), while in others, there is a gradual drop and prolongation of the time required before the pO_2 numerically falls below the pCO_2 numerically. This point we have, in our studies, defined as "crossing". In some cases the pCO_2 (Figures 15 and 16) plateaus for a variable period of time only to be followed by an abrupt rise. Table II lists in more detail the times involved in the various phases following airway restriction to death. The period of "crossing" from initiation of airway restriction varies from 8 to 147 minutes. Many factors, either singly or in combination, may be responsible for these variations. The health and nutritional status of the animals has been noted on occasion to influence the variation in this period. Animals with upper respiratory infections do not tolerate asphyxia as well as in the normal state and certainly those with lower respiratory tract infections succumb quickly. On occasion a lobar pneumonia has been noted. Age plays a great part, the younger the animal, the more resistant it is to sudden changes in blood-gas values with asphyxia. The breed of the animal has some influence, i.e., Beagles appear to be very hardy and resistant to sudden changes in their blood-gas picture with asphyxia. Sex does not appear to play a great part in the pre-crossing phases but certainly the size of the animal would be expected to play a great part as the airway restriction was of a constant size irregardless of whether the

animals were large or small. In general, this did not seem to be so as some of the larger animals took far longer to show respiratory embarrassment than some of the smaller animals. Perhaps some of the other factors were playing a part as well.

Despite the number of variables introduced as regards to age, weight, sex, breed, health and nutrition the phase to death, following "crossing" of the blood gases remains relatively constant and lends some support to its use for oxygenator assessment.

An arbitrarily set period of time following airway restriction cannot be used as the point at which to initiate partial cardio-pulmonary bypass if the results are to have any validity. Animal Number E-643 (Figure 15) illustrates this well. In this animal, at one hour post airway restriction, there is a blood-gas pictures which shows signs of stabilizing, and one in which the blood-gas values are not drastically abnormal. In comparison, Animals E-1236 and E-1262 died prior to one hour after airway restriction. Only one out of three animals survived long enough to be put on partial cardiopulmonary bypass if one hour post airway restriction was our criteria for instituting bypass. Although this example is extreme, any set post airway restriction time which is to be used at the point to initiate bypass assist is not without influencing the results.

If we now focus our attention on the period following "crossing", that is, when the blood-gas pO_2 value is numerically lower than the pCO_2, we find a more predictable time to death. Table II shows the time from "crossing" to death. This varies from 35 - 61 minutes with a mean of 48 minutes. Figure 17 separates the phases from airway

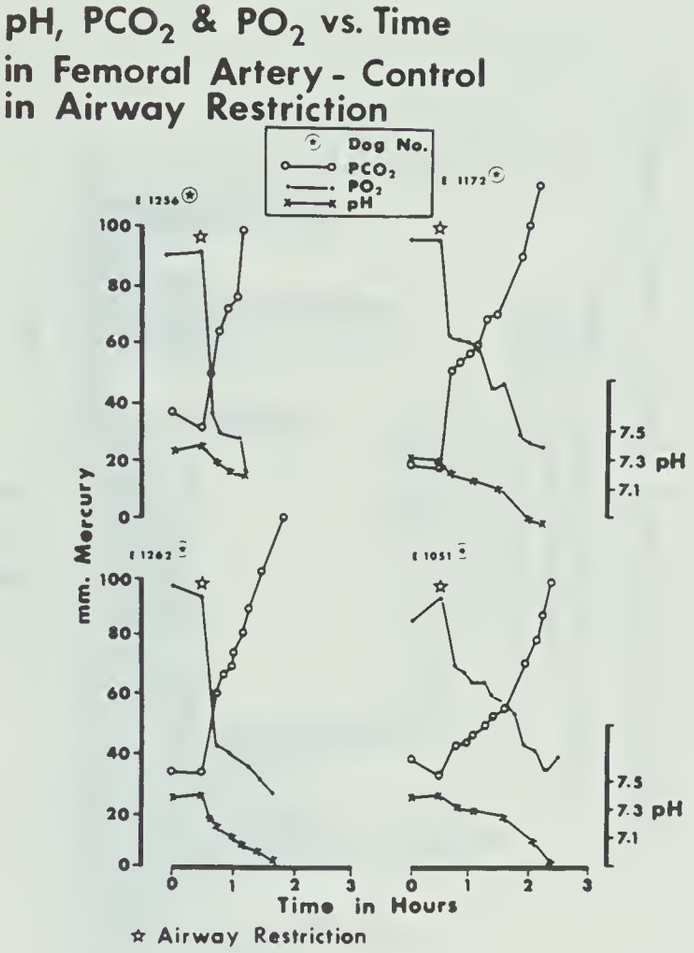

Figure 14.

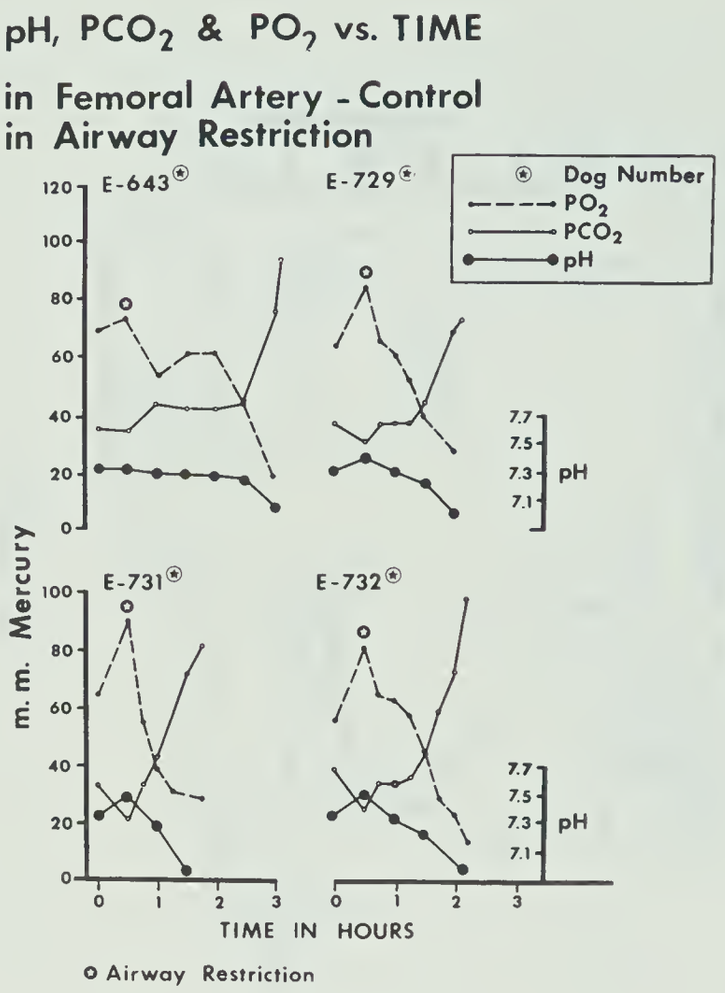

Figure 15.

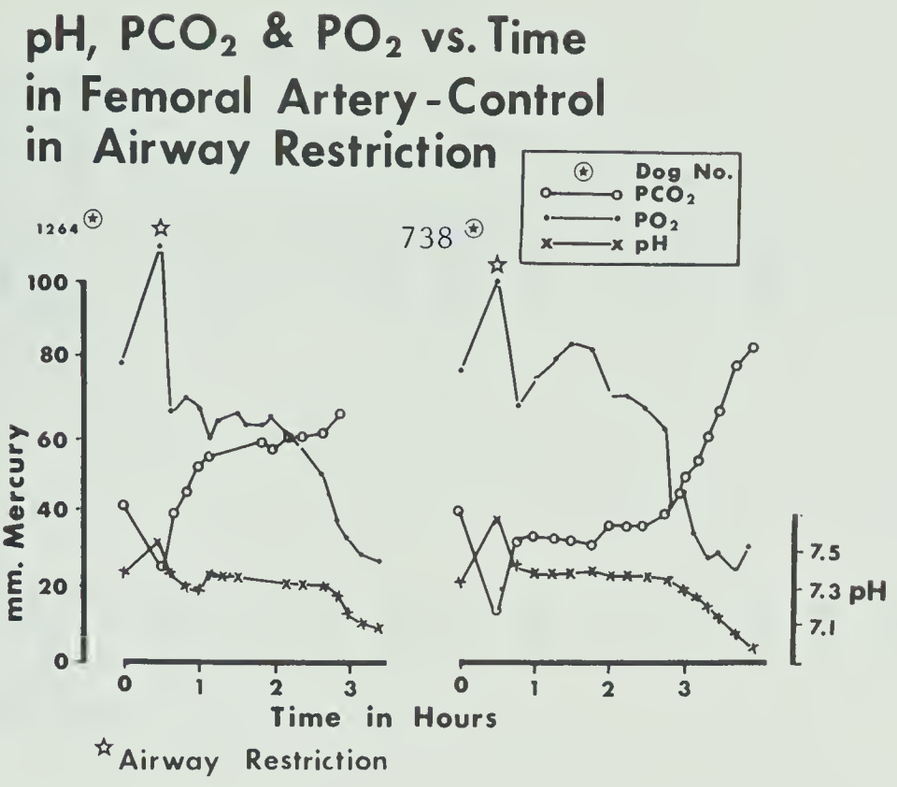

Figure 16.

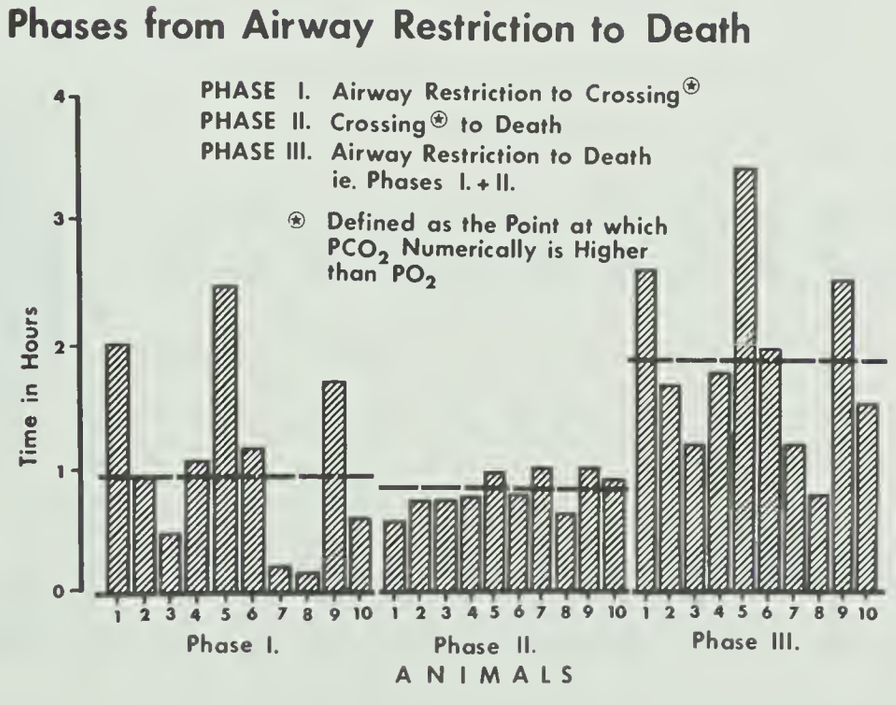

Figure 17.

TABLE II: CONTROLS - GROUP I

ANIMAL	AIRWAY RESTRICTION TO PO_2 LESS THAN PCO_2 (mins.)	VALUE AT WHICH $PO_2 = PCO_2$ (mm Hg)	$PO_2 = PCO_2$ TO DEATH (mins.)	AIRWAY RESTRICTION TO DEATH (mins.)
E 643	120.0	45.5	35.0	155.0
E 729	56.0	42.0	43.0	99.0
E 731	27.0	41.5	43.0	70.0
E 732	60.0	43.0	45.0	105.0
E 738	147.0	46.5	57.0	204.0
E 1051	70.0	54.0	46.0	116.0
E 1262	10.0	52.0	60.0	70.0
E 1256	8.0	46.5	37.0	45.0
E 1264	100.0	58.5	61.0	161.0
E 1172	35.0	58.5	55.0	90.0
Mean Value	56.3	48.8	48.0	111.5
Standard Deviation	44.9	6.16	8.92	46.3

restriction to death. Phase I - airway restriction to "crossing" shows graphically the marked variability among animals. This variability is reflected again in Phase III as this is a composite picture of Phase I and II. Phase II - "crossing" to death - shows a much more consistent picture among the various animals and because of this the "crossing" of the blood-gases affords the best time in which to initiate partial cardiopulmonary assist without drastically influencing the final outcome.

B. Membrane Oxygenator Assessment

Figure 18 shows the blood-gas picture for five animals placed on partial cardiopulmonary bypass (30 cc./kg. body weight flow/min.) following the "crossing" of blood gases. It is felt that this point of assist would more closely approximate the clinical situation of acute respiratory distress and be more predictable as to the expected period of survivability without assist. As opposed to this above group of five animals, a group of six animals (Figures 19 and 20) were placed on bypass at the time of airway restriction. The institution of partial cardiopulmonary bypass at the time of inducing respiratory distress has been used by other investigators and is performed here to show how the results are influenced. By instituting the bypass at the point of "crossing" survival has been prolonged from 48.0 minutes to 179 minutes beyond this point (Table III).

The effect of putting animals on partial cardiopulmonary bypass at the time of airway restriction (prophylactic oxygenation) is seen in Figures 19 and 20 and summarized in Table IV. Three animals

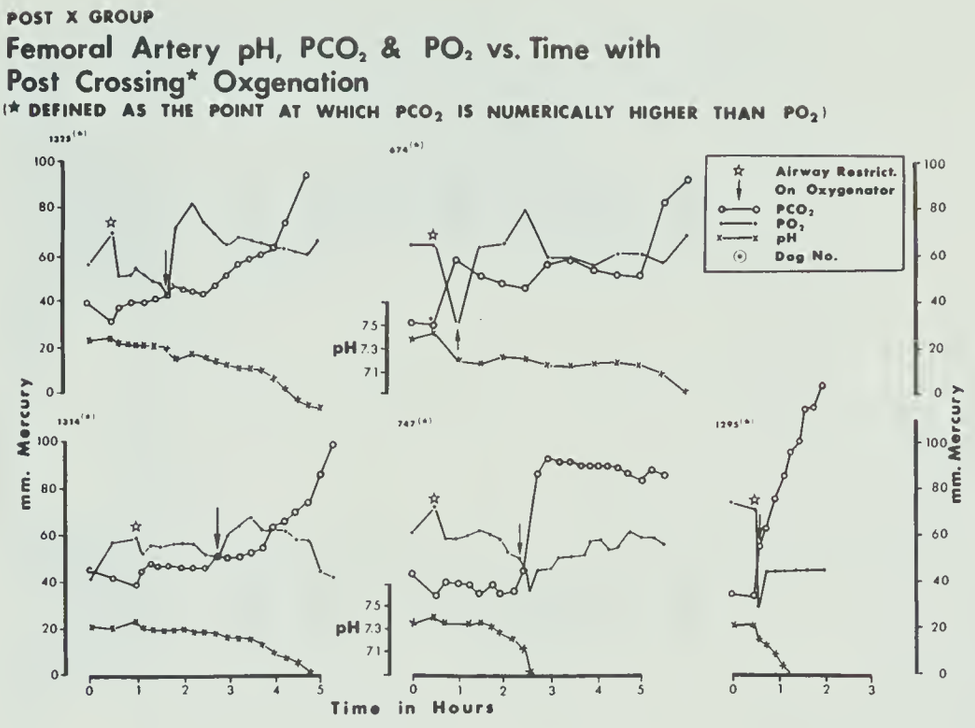

Figure 18.

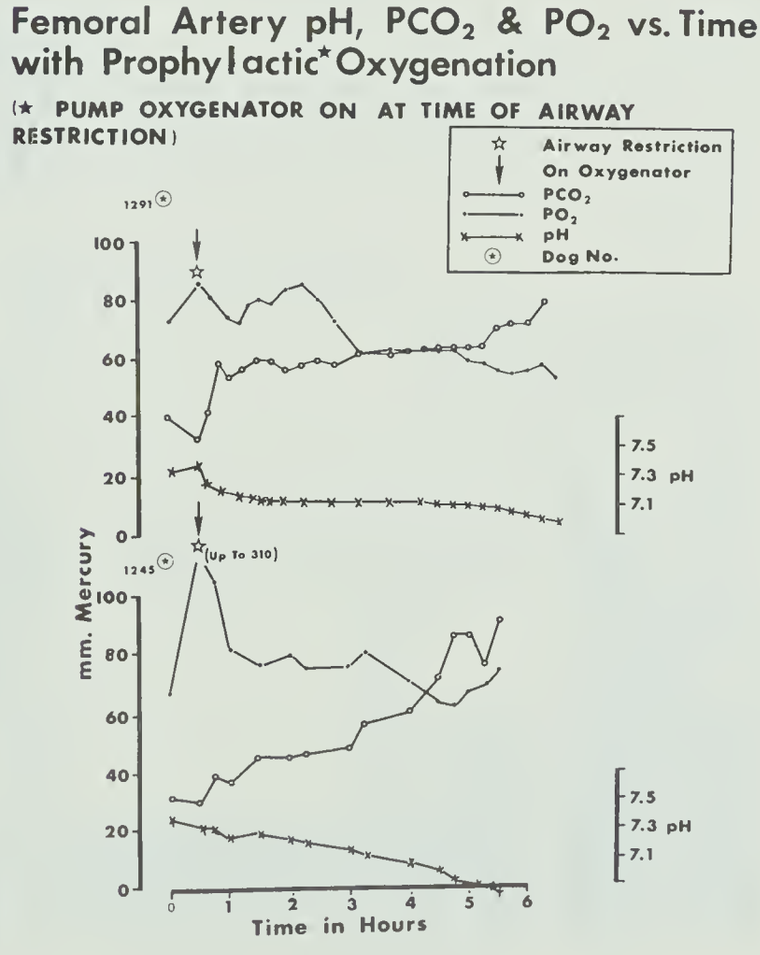

Figure 19.

TABLE III: PERFUSION AFTER CROSSING OF PO_2 & PCO_2

ANIMAL	AIRWAY RESTRICTION TO PO_2 LESS THAN PCO_2 (mins.)	VALUE AT WHICH $PO_2 = PCO_2$ (mm Hg)	$PO_2 = PCO_2$ TO DEATH (mins.)	AIRWAY RESTRICTION TO DEATH (mins.)
E 674	16.5	45.5	285.0	301.5
E 747	115.0	44.5	182.0	297.0
E 1295	3.5	44.0	78.0	81.0
E 1325	70.0	43.0	195.0	265.0
E 1314	105.0	51.0	155.0	260.0
Mean Values	62.0	45.6	179.0	241.0
Standard Deviation	31.96	1.97	66.75	57.7

Time From $PO_2 = PCO_2$ to Death

1. Control Group
   (a) Standard Deviation 8.92
   (b) Mean 48.0
2. Perfused After "Crossing"
   (a) Standard Deviation 66.75
   (b) Mean 179.0

Difference between Means = 131.0
Standard Error = 29.98 ∴ Statistically significant.

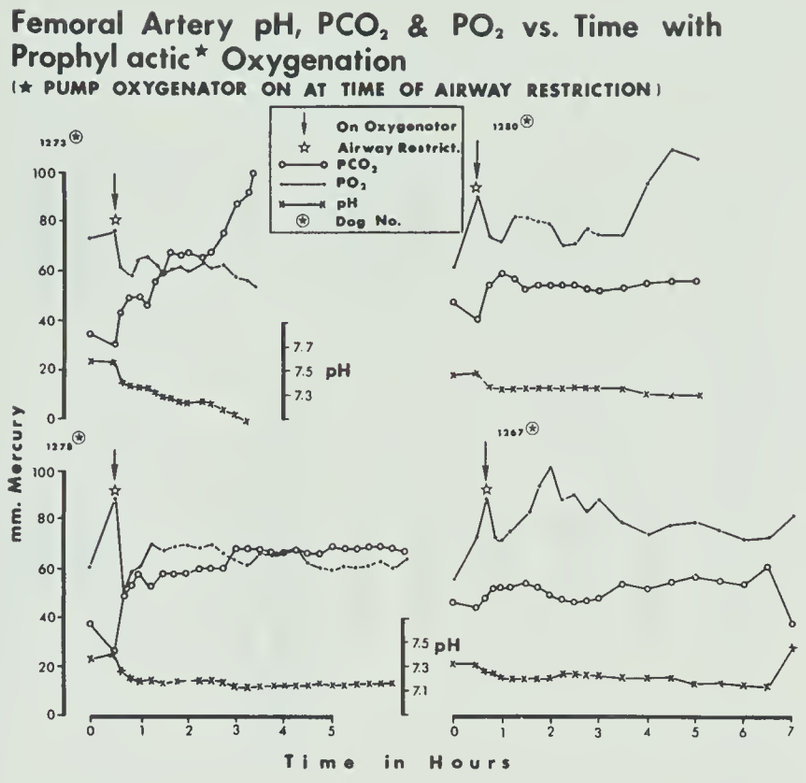

Figure 20.

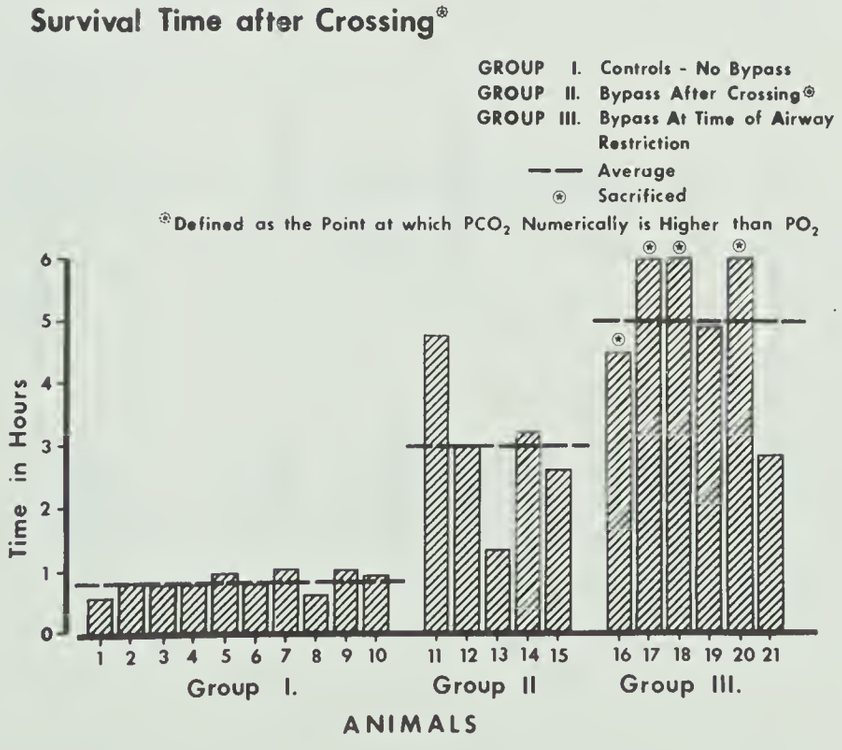

Figure 21.

TABLE IV: PERFUSION AT TIME OF AIRWAY RESTRICTION

ANIMAL	AIRWAY RESTRICTION TO $PO_2 = PCO_2$ (mins.)	CROSS VALUES (mm Hg)	CROSSOVER TO DEATH (mins.)	PERFUSION (hours)
E 1280	No Crossover	-	Sacrificed Membrane Devel. Leaks	4.50
E 1291	170.00	63	Survived	6.00
E 1267	No Crossover	-	Survived	6.00
E 1245	3.75	66	75.00	4.92
E 1273	57.00	59	123.00	2.83
E 1278	10.00	62	Survived	6.00

survived six hours of partial cardiopulmonary bypass with airway restriction and, no doubt, would have survived much longer had it not been arbitrarily decided to limit bypass to six hours. One animal, while in very good condition, had to be sacrificed at four and one-half hours due to membrane leaks developing in the oxygenator. This animal, it was felt, would certainly have survived six hours. One animal survived four hours and 55 minutes, another two hours and 50 minutes. No mean value was established as limits were set on the duration of cardiopulmonary bypass. Of note is that two of the animals in this series did not show "crossing".

The survival time following "crossing" of the blood-gases in the three groups of animals used in this study is summarized in Figure 21. The control group shows a consistent period from "crossing" to death, Group II, with "post-crossing" oxygenation, shows a prolongation by partial cardiopulmonary bypass; and Group III, with partial cardiopulmonary bypass instituted at the time of airway restriction (prophylactic oxygenation) shows a further prolongation of survival.

C. Pump-Oxygenator Blood Distribution Studies

1. Cerebral Tissue pO_2 Responses. The use of the polarographic microelectrode technique for measuring tissue oxygen tensions has been a controversial matter for some time. In some reports the results have been expressed in terms of millimeters of mercury oxygen pressure (24,29,97) whereas many other investigators (79,83,87,94,132,178) have been unable to obtain precise oxygen tension calibration in tissues. Some authors (162,163) refer to the measurement in tissues as being one of oxygen availability rather than of oxygen tension,

and this is probably wise when no attempt has been made to calibrate the electrodes in that particular tissue. Uncalibrated electrodes may be used to gather useful information about changes in oxygen tension. If this is done the results are better expressed as percent of initital stable values. Although no attempt is made to interpret amerage (expressed as galvanometric units) in terms of oxygen tension (expressed as millimeters of mercury), nevertheless, an increase or decrease in galvanometric units corresponds to a proportionate increase or decrease in oxygen tension (79).

Oxygen tension levels obtained by this equipment are a reflection of the flow of current through the electrode as a result of reduction of oxygen molecules at the cathode. These levels were expressed as arbitrary units which represented the readings on the gas analyzer. Precise calibration of oxygen tension levels in tissues cannot be obtained by the technique used in these studies. Arbitrary units were obtained during the experimental period on control or normal states, after asphyxia and during bypass treatment.

Previous workers, with experiences involving more than 500 procedures, feel that this equipment cannot be used for determining precise oxygen tension levels in terms of millimeters of mercury. However, they feel gross changes in tissue pO_2 levels can be detected with the polarographic microelectrode and reproducible results obtained and that the magnitude of change as compared to control levels can be quantitated. With this system it is possible to compare the effects of several different techniques in raising oxygen tension in normal and diseased tissues.

The electrode is a delicate instrument and preparation for use and maintenance during an experimental study is difficult. Polarography has certain inherent and definite limitations (35,41). When the active surface of the electrode is exposed to protein solutions the diffusion current decreases at a rate of approximately 5% per hour, depending upon the protein concentration in the solution (95). This effect is considered to be both a passive depositing and active electroplating of protein into the platinum surface. Also, the base level of the current in protein solutions is always lower. This is attributed to the increased viscosity of the protein solutions (29,95). Small changes in the readings could result from temperature changes (87,103, 133). If the electrode moves there is a change in current (87,132), usually an increase that results from a more rapid supply of oxygen from fresh tissue broughtadjacent to it, and because of this, it is advisable to avoid comparisons of oxygen tensions measured with repeated insertions of the electrode unless many electrodes are employed and the mean of the readings is used (132).

A loss in sensitivity can occur with localized bleeding, fat or fibrin deposition, or precipitation of electrolytes in the vicinity of the tip of the electrode. There is also a gradual decrease that occurs in readings due to the deposition of insoluble salt precipitates on the membrane.

Since the diffusion coefficient of the brain is unknown, Meyers and his group prefer to use the term oxygen availability, as suggested by Montgomery and Horwitz (133). Their experiences with the polarographic microelectrode technique indicates that the local tissue changes of

oxygen in the brain may be extremely rapid and comparable to rates of change found in saline solutions (129). The assumption that the measurement at the electrode directly reflects oxygen availability in the tissue immediately surrounding the electrode appears to be justified. Bronk and associates (24) noted that alteration in the composition of inspired air or in the pattern of respiration was promptly reflected in the oxygen tension of the cortical extravascular regions. These authors also noted that any change in the cerebral flow through the cortex has an immediate effect upon the gradients of tension and upon the concentration of oxygen at any one point. Davies, McCulloch and Roseman (42) have observed a fall in oxygen content of the cat cerebral cortex during Metrazol convulsions unassociated with change in blood pressure. This latter was confirmed by Davies and Remond (43). Rapid fluctuations in oxygen tension of the brain, produced by alteration of the oxygenation and circulation of the blood, were also found by Davies, McCulloch and Roseman (42). Respiratory anoxia, secondary to general vasodilation, produced a fall in cortical oxygen levels. Experimental studies with the polarographic technique in monkey cortex (51,127,129) and later in man (128), have demonstrated the high oxygen consumption and small oxygen reserve of healthy cerebral tissue.

Early consequences of cerebral ischemia appear to be due to local hypoxic damage to neurons (126,129), which may be reversible if a minimal blood flow is preserved. Once neuronal injury has occurred, the tissue demand for oxygen is greatly reduced, since metabolically paralyzed or infarcted brain has a minimal oxygen consumption (50,51, 126,128,130).

Oxygen polarography appears to be a reliable method for continuous recording of oxygen availability in cerebral tissue spaces in vivo. After prolonged ischemia the oxygen electrode records local oxygen changes, due not only to diminished blood supply, but also to the dimished utilization of oxygen by damaged tissue (129).

To date, studies regarding brain tissue oxygen tension with partial cardiopulmonary bypass have been lacking in the literature. One aspect of this study was to observe, in particular, the cerebral tissue pO_2 response to the various bypass procedures; i.e. aortic root, axillary artery and femoral artery return routes, as well as veno-veno bypass with external jugular vein return during respiratory distress.

The amount of oxygen present in a tissue is a function of:

1. The rate at which arterial blood is delivered to the tissue.
2. The amount of oxygen present in the arterial blood.
3. The rate at which oxygen is being consumed by the tissue.
4. The diffusion coefficient of oxygen in tissue fluids.

The first three of these factors and possibly the fourth are related to a large number of physiological variables. Some of the more important are:

1. Oxygen concentration in inspired air.
2. Alveolar ventilation.
3. Oxygen carrying capacity of the blood.
4. Cardiac output.
5. Blood pressure.
6. The state of the peripheral vasculature.

7. The presence or absence of calorigenic substances such as anesthetics, epinephrine and thyroxine.

The results obtained deal only with oxygen tension and do not indicate whether the tissue can utilize the oxygen that is present. Nor do they indicate whether the amount of oxygen present, if it can be utilized, is adequate to maintain normal cellular function and respiration under normal conditions.

The subsequent figures show the cerebral tissue oxygen tension responses following airway restriction with a #14 needle and the secondary responses with institution of partial cardiopulmonary bypass for a period of one and one-half hours. The pre-asphyxia cerebral tissue oxygen tension, i.e., control, is expressed as normal or 100%. The subsequent gas analyzer readings are expressed as a percentage of this.

Figure 22 illustrates a partial cardiopulmonary bypass with a femoral artery return route. It was expected and confirmed that little or none of the benefits normally accrued from extracorporeal circulation are seen in the cortical areas as evidenced by the steady decline in all five animals of cerebral oxygen pO_2 tension. Cardiopulmonary bypass was instituted at the point of "crossing" as previously defined.

Figure 23 shows the response to partial cardiopulmonary bypass with a right axillary artery return route. A drop in cerebral tissue pO_2 tension with respiratory distress and the marked and very immediate increase with the initiation of the partial bypass assist is noted.

Figures 24 and 25, each containing another five animals, show the cerebral tissue pO_2 tension response with respiratory distress

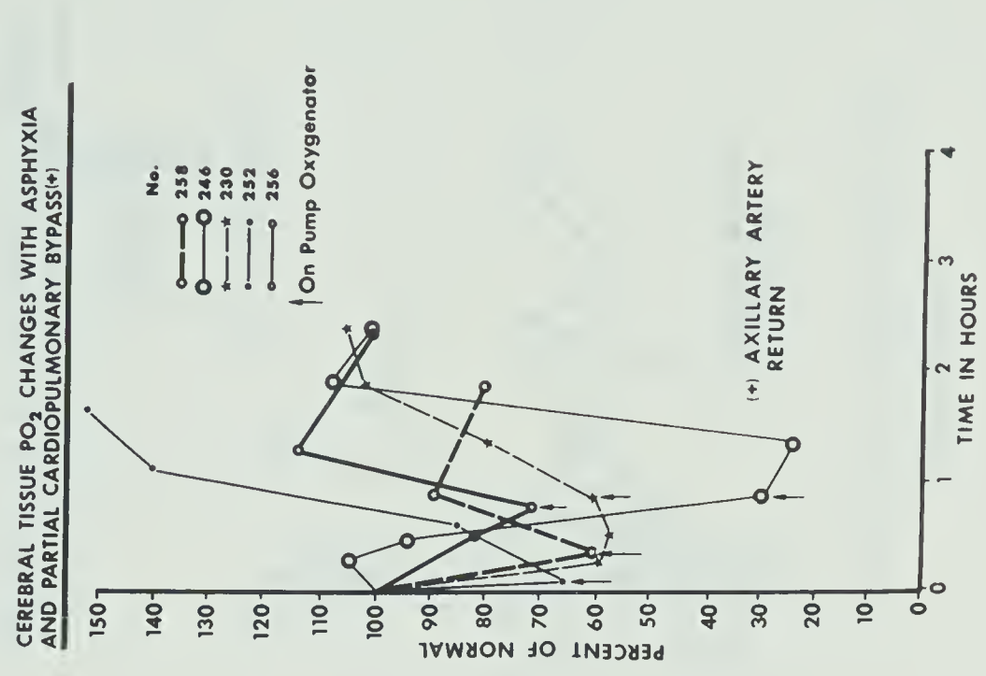

Figure 23.

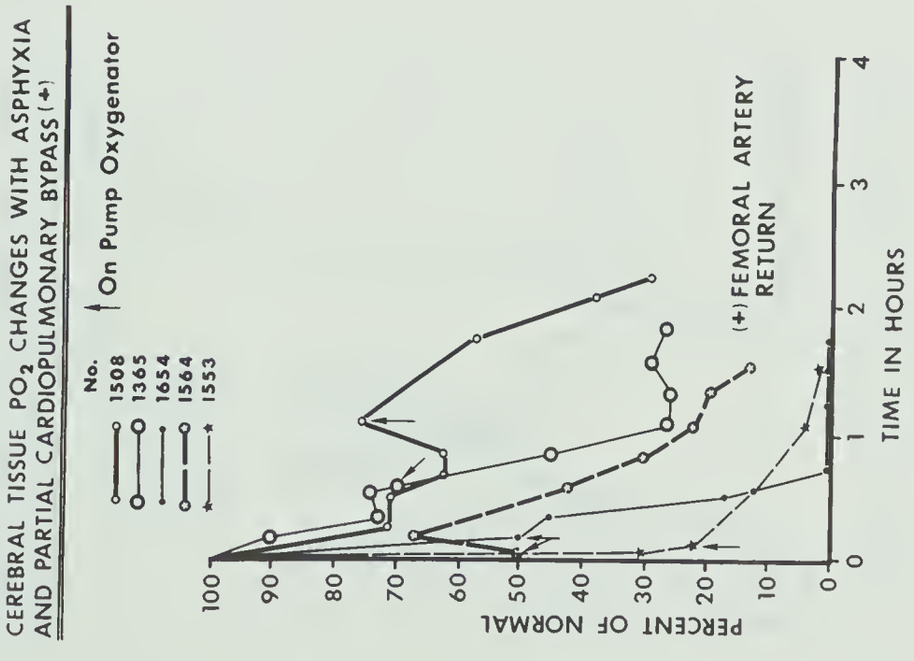

Figure 22.

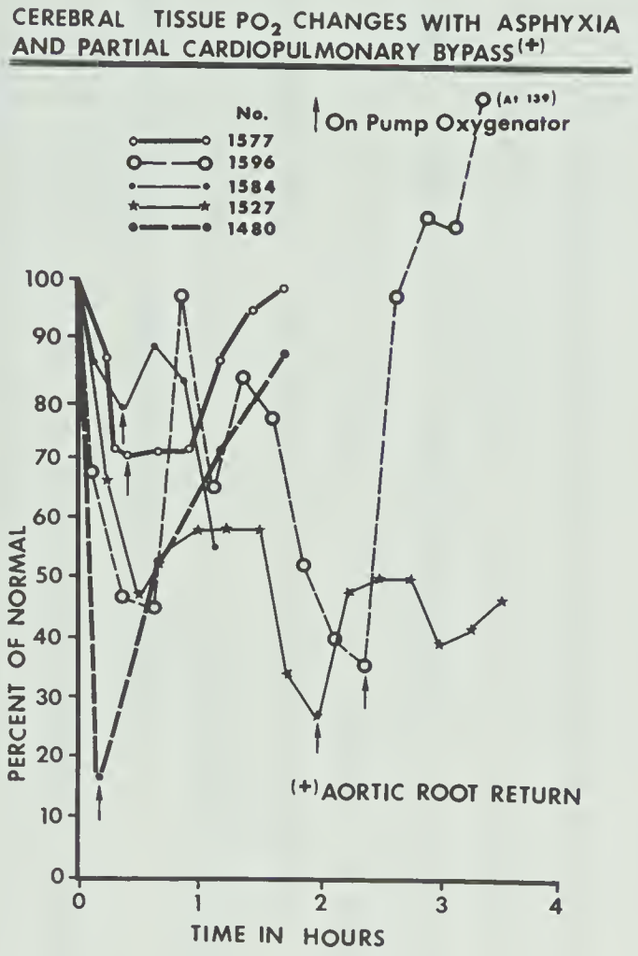

Figure 24.

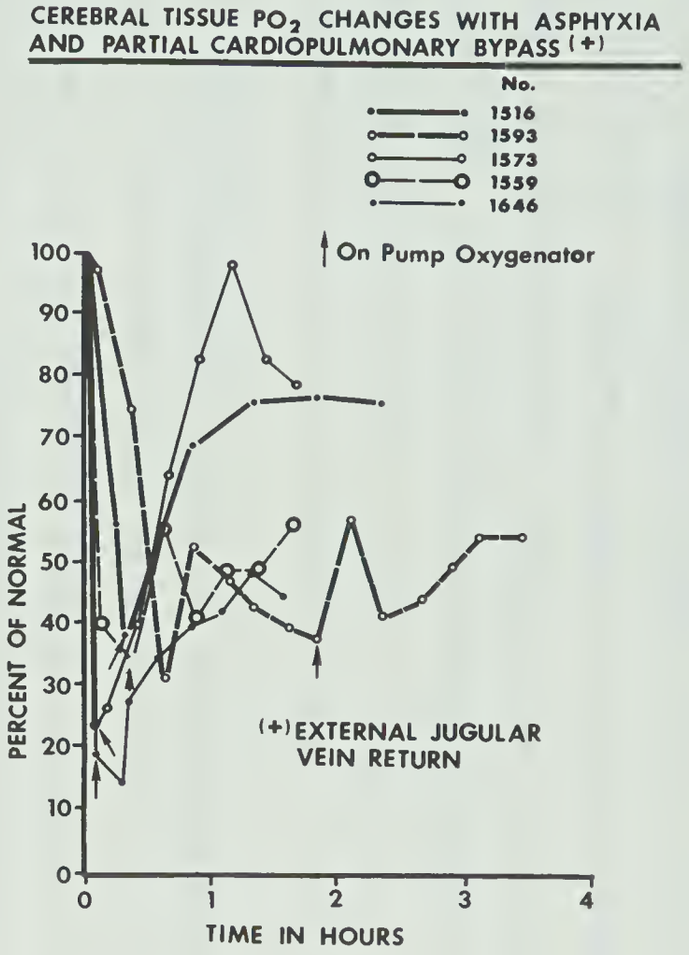

Figure 25.

followed by partial cardiopulmonary bypass assist with an aortic root return and a veno-venous bypass utilizing the left external jugular vein return route. Responses in these two are not as dramatic as in the former two but satisfactory cerebral tissue pO_2 tension improvements are noted. It is felt that no consistent difference exists between these latter two methods. Further comment will be reserved until presentation of the data obtained in part 2 of this study.

2. Pump-Oxygenator and Cardiac Dye Distribution Studies. The utilization of the tracer concept, as of late, involves primarily isotopic methodology and the history has been reviewed by Hevesy (32). Because of the costs of instrumentation, extra personnel required, radiation hazards and regulations regarding the use of radioactive materials, we have attempted to use one of the dyes which has received widespread application in the field of cardiac and circulatory studies.

The dye chosen was Cardio-green (Indocyanine Green) because it has its peak spectral absorption at 800 mu., a wavelength equally absorbed by oxygenated and reduced hemoglobin, and which thereby permits the continuous recording of dilution curves in whole blood without interference from variations in blood saturation. This was of extreme importance in our studies on respiratory distress as wide variations in oxygen saturation were expected.

Rapid distribution of the dye is also essential for the technique of continuously recorded dye-dilution curves, and in order to be suitable for quantitative purposes, an indicator must not be lost from the

bloodstream during the initial circulation through the heart and lungs. The latter property is generally achieved through binding of the indicator molecules by plasma proteins. Conversely, it is preferable for many purposes (except the determination of blood volume) that the indicator leave the bloodstream (preferably completely) after its first circulation, thus avoiding build-up in its concentration in the blood following repeated injection of the indicator. Cardio-green rapidly leaves the circulation as the half time is approximately ten minutes (65,182), and clearance is almost totally by the liver with the free unbound dye being completely recovered in the bile. Rapid stabilization of the dye has been shown by Bassingthwaighte and co-workers (5).

The peak concentration attained by the dye-dilution curves depends upon the amount of dye injected and on the specific site of sampling. A high concentration of dye produces a tall peak and a distal sampling site a short peak because of fractionation and dilution of the dye particles.

Since Indocyanine Green binds to proteins, injection into the pump-oxygenator line, in effect, labels a bolus of pump-proteins which are expected to reflect the distribution of the other pump-blood elements, i.e., oxygen. Single injection techniques label but a small proportion of these, and by performing dye-dilution curves at femoral and carotid artery levels, proportioning of these pump-proteins may be ascertained by the peak concentration of the dye curves. Since the pump-oxygenator system supplies a constant source

of oxygen, a comparable situation would exist with a constant infusion of pump-oxygenator line labelled proteins. Barring build-up, re-circulation and the pulsatile nature of the circulation, which would be reflected by irregularities in our trace, a constant dye infusion would produce a trace showing plateaus of varying heights in different sampling areas. Providing cardiac output and blood flow did not change between samplings, a direct comparison of the curves could be made and a gross proportioning of the pump-oxygenator blood obtained.

Table V summarizes the pertinent data on five animals subjected to partial cardiopulmonary bypass for respiratory distress with a femoral artery return. Following "crossing" of the blood-gases and one-half hour of partial cardiopulmonary assist, dye-dilution curves were performed.

Blood flow rates at each level for both line and right ventricular dye injections are close enough to allow direct comparison of peak curve heights. Figure 27 (Animal Number F-186) portrays the dye-dilution curves obtained with a femoral artery return route and is representative of the group.

Routine right ventricular injection results in the appearance of the dye in the carotid arteries. No dye appears at the femoral level with a similar right ventricular injection. As confirmation of this, injection of dye into the pump return line shows a marked concentration of dye in the opposite femoral artery with no appearance of dye at the carotid level. This picture suggests that a femoral artery partial cardiopulmonary bypass of 30 cc. flow/kg. body weight results in no

TABLE V: FEMORAL ARTERY BYPASS RETURN

ANIMAL	DYE CONC. (mg)	Femoral Artery Level				Carotid Artery Level			
		R. Ventricular Injection		Line Injection		R. Ventricular Injection		Line Injection	
		FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)
F 123	2.5	58.0	0	62.0	10.6	188.0	3.70	184.0	0
F 143	2.5	58.0	0	62.0	12.6	170.0	4.30	168.0	0
F 186*	2.0	76.0	0	81.0	14.05	174.0	4.85	174.0	0
E 1407	2.0	55.0	0	55.0	8.7	242.0	4.40	250.0	0
F 116	2.5	69.5	0	69.5	11.1	131.5	5.10	137.0	0

* Dye curves depicted in Figure 27.

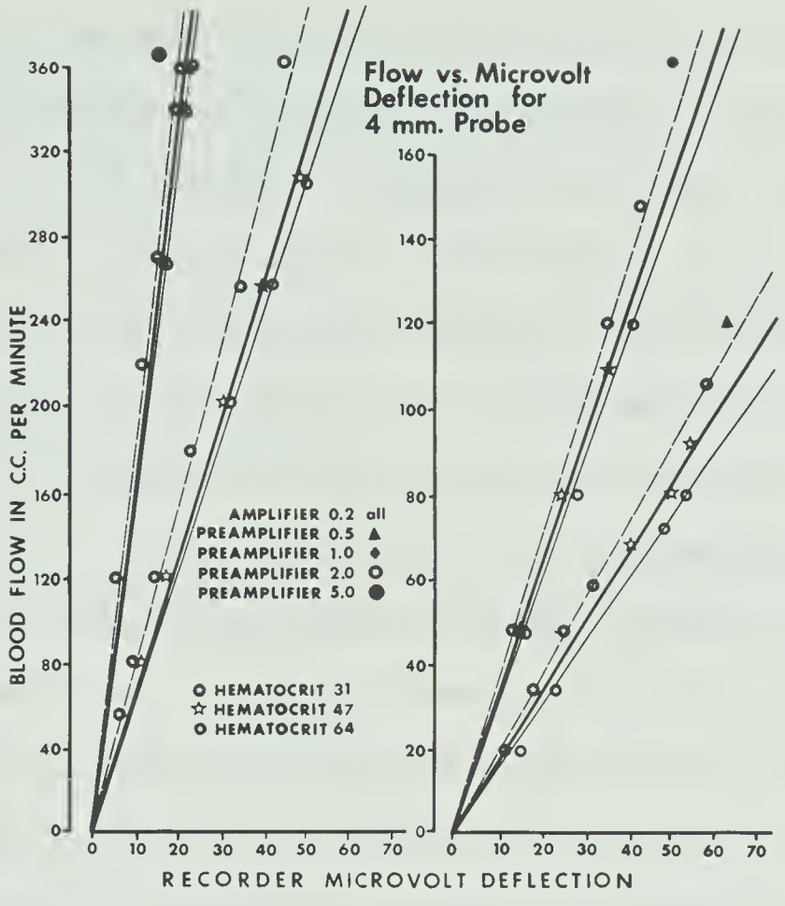

Figure 26. Flow Probe Calibration.

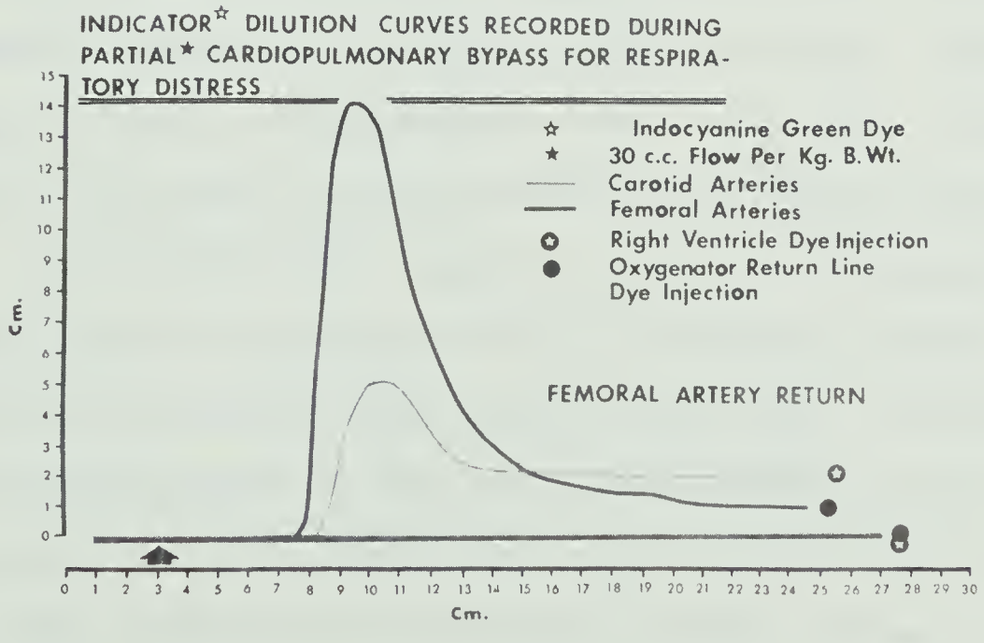

Figure 27.

distribution of the pump-oxygenator blood at or above the aortic arch. This picture supports the previous study showing a continual decrease of cerebral pO_2 with respiratory distress and partial cardiopulmonary assist utilizing a femoral artery return (Figure 22) and implies that pump-oxygenator blood flow becomes reversed in the abdominal aorta by the proportion of cardiac output that is directed from the heart down the aorta. The effects of two oppositely directed bloodstreams is to slow one and halt or reverse the other. The pump-oxygenator stream with a femoral artery return slows the normal blood flow from the heart down the aorta. A similar volume of blood flow can only be accommodated by directing an increased amount of the cardiac output through the great vessels of the aortic arch and at increased velocity. Table V shows such a picture with increased carotid artery flow with a femoral artery return site.

Although cerebral blood flow is increased, little benefit is derived due to the marked oxygen desaturation of this blood.

Table VI summarizes the data on another group of five animals subjected to a right axillary artery return route bypass. Typical of the group is Figure 28 (Animal Number F-68). In general, the data obtained is the inverse to that obtained for the femoral artery return route. At the carotid level, injection of dye into the bypass return line shows a good concentration of dye in the carotid arteries, while very little is visualized at the femoral artery level. As expected, right ventricular injection shows very little evidence of dye at the carotid level, the main concentration being detected at the femoral level. This corresponds with the previous cerebral perfusion studies,

TABLE VI: AXILLARY ARTERY BYPASS

ANIMAL	DYE CONC. (mg)	Femoral Artery Level				Carotid Artery Level			
		R. Ventricular Injection		Line Injection		R. Ventricular Injection		Line Injection	
		FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)
F 68*	2.0	60.0	1.30	58.0	0	73.0	0	116.5	9.3
F 179	2.5	51.5	1.50	71.0	5.20	89.5	1.9	87.0	4.7
F 97	2.5	84.0	1.85	87.0	1.40	192.0	0	188.5	9.1
F 168	2.0	230.0	3.50	230.0	0.78	290.0	0	285.0	4.5
F 88	5.0	80.0	3.05	80.0	0.85	97.0	2.1	101.0	9.1

* Dye curve depicted in Figure 28.

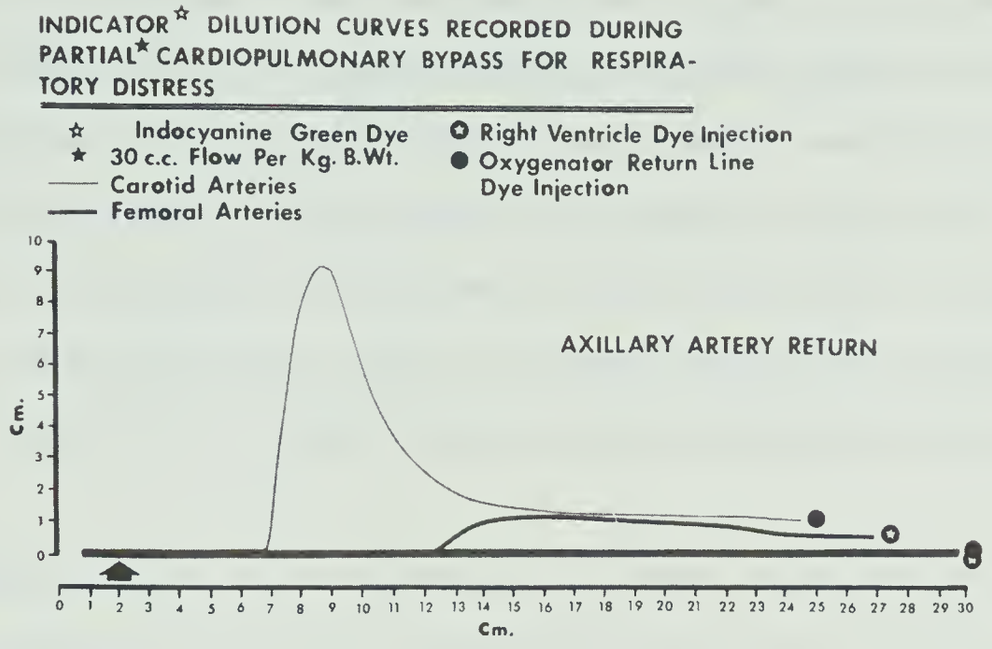

Figure 28.

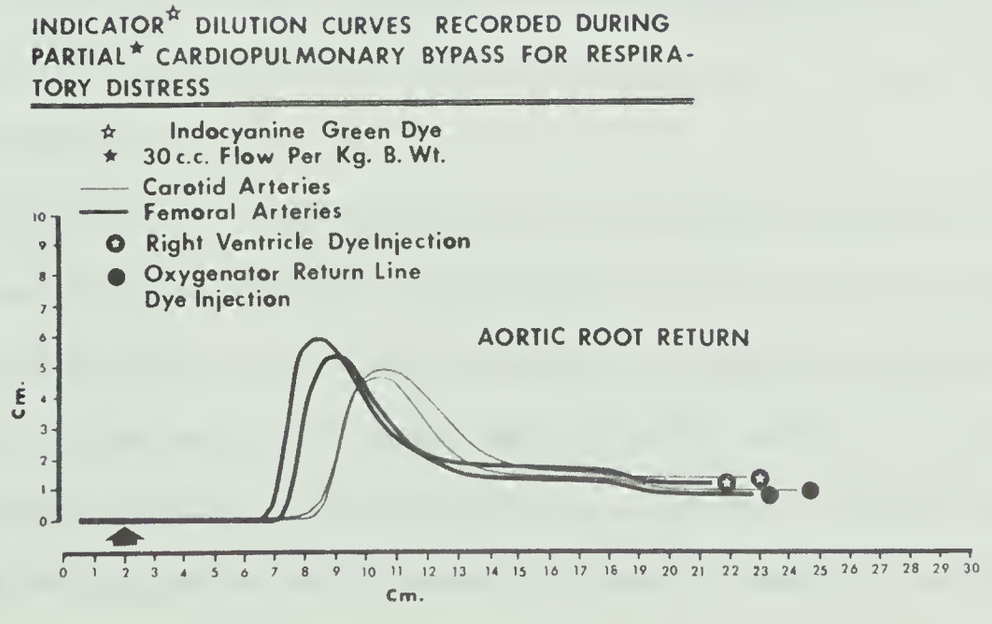

Figure 29.

(Figure 23) utilizing a right axillary artery bypass return route. In Animal Number F-179, the femoral level curve peak heights are completely opposite to what is expected. It is certainly possible that other physiologic factors may have played a part here, or human error, as perhaps the dye curves obtained were labelled incorrectly. Results in the other four animals tend to indicate, that with an axillary artery return route, cerebral and presumably myocardial perfusion is good.

This is explained on the basis of a common origin for the right common carotid artery and the right subclavian artery which forms the axillary artery distally. This common origin, the brachiocephalic trunk, receives all pump-oxygenator blood returning via the right axillary artery. Two paths exist for this pump-oxygenator flow; (1) up the right carotid artery, and (2) down and through the origin of the brachiocephalic trunk into the aortic arch. This latter route is opposed by the cardiac output and its anterograde flow from the aorta. The line of least resistance for retrograde axillary and subclavian blood flow is up the right carotid artery after entering the brachiocephalic trunk.

Since the left subclavian and its continuation, the left axillary artery are separate from the left common carotid artery, and since the orifice of the left common carotid artery is upstream from that of the left subclavian, we cannot expect any or little cerebral flow from a bypass using the left axillary artery as a return. In fact, left axillary artery return would probably primarily result in an abdominal aortic distribution of pump-oxygenator blood.

Table VII presents the data obtained utilizing an aortic root return for the bypass. Figure 29 (Animal Number E-1408) is a representative sample of the group. In this group there is no consistent trend as to the distribution of the dye particles. Instead, it appears that distribution is adequate at both femoral and carotid levels. Variations may be due to the last few centimeters of placement of the tip of the return catheter. In one instance, carotid level dye concentration is greater than that at the femoral level, in another animal we find the opposite of this. Most unexpected were the figures at the carotid level for Animal Number F-145. Here, the values are much like that for the axillary artery return bypass. It may be that the tip of the bypass return line may have been at the root of the carotids, and subsequently, repositioned with cardiac movement as the change is not reflected in the femoral level traces. From this data, it could be expected that cerebral and myocardial perfusion would be similar to that downstream from the aortic root. This is also supported by the cerebral tissue pO_2 response, seen in Figure 24, with an aortic root bypass return.

Table VIII summarizes the results obtained in a group of five animals placed on a veno-veno bypass with an external jugular vein return route. Figure 30 (Animal Number F-188) is a representative sample of the group. A uniform trend is noted of dye particle distribution not unlike that seen for an aortic root infusion. This similarity is also noted in the cerebral tissue pO_2 studies for an aortic root return (Figure 24) and veno-veno bypass utilizing an external jugular vein return route (Figure 25).

TABLE VII: AORTIC ROOT BYPASS RETURN

ANIMAL	DYE CONC. (mg)	Femoral Artery Level				Carotid Artery Level			
		R. Ventricular Injection		Line Injection		R. Ventricular Injection		Line Injection	
		FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)
F 104	1.25	57.0	0.65	58.5	1.70	MISSED		111.0	1.45
F 164	5.00	41.0	6.26	38.5	1.92	74.5	6.30	89.0	2.68
E 1408*	2.50	55.5	4.65	55.5	5.90	111.0	4.90	111.0	5.40
F 145	2.00	92.0	1.90	83.0	3.40	200.0	0	200.0	9.05
F 126	2.50	NOT OBTAINED				158.0	2.05	150.0	4.90

* Dye curves depicted in Figure 29.

TABLE VIII: EXTERNAL JUGULAR VEIN BYPASS RETURN

ANIMAL	DYE CONC. (mg)	Femoral Artery Level				Carotid Artery Level			
		R. Ventricular Injection		Line Injection		R. Ventricular Injection		Line Injection	
		FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)	FLOW (cc/min)	CURVE Height (cm)
F 40	2.0	25.0	1.40	26.5	1.20	100.0	3.55	88.0	2.40
F 48	2.0	44.0	2.26	38.5	1.65	79.0	3.50	82.0	2.70
F 188*	2.0	63.0	1.90	67.5	1.30	292.0	3.80	301.0	2.15
F 178	2.5	22.5	2.80	24.0	2.60	49.0	2.10	49.0	3.50
F 133	2.5	84.0	2.40	87.0	1.40	189.0	3.10	189.0	3.05

* Dye curve depicted in Figure 30.

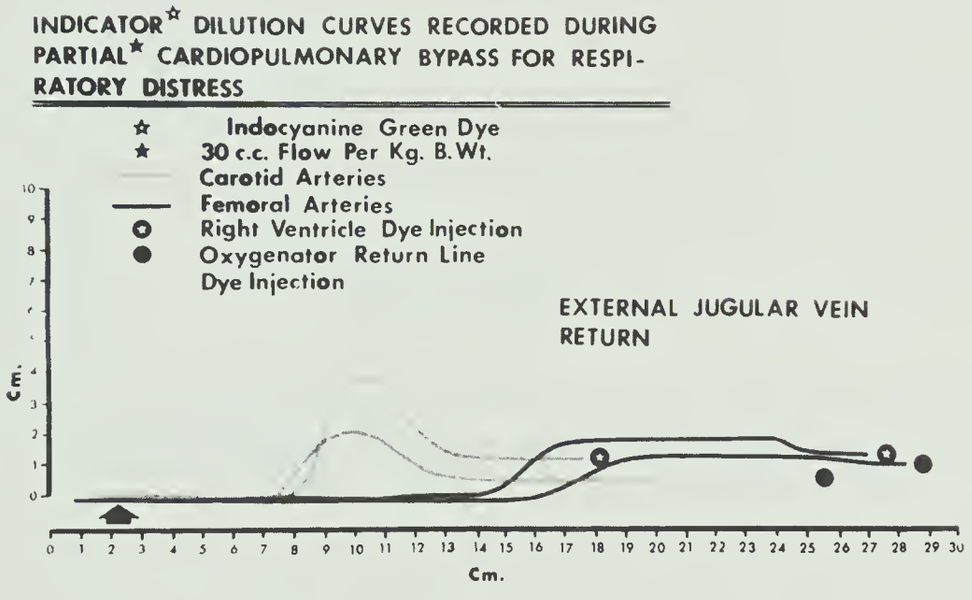
INDICATOR☆ DILUTION CURVES RECORDED DURING PARTIAL★ CARDIOPULMONARY BYPASS FOR RESPIRATORY DISTRESS
☆ Indocyanine Green Dye
★ 30 c.c. Flow Per Kg. B.Wt.
Carotid Arteries
Femoral Arteries
Right Ventricle Dye Injection
Oxygenator Return Line Dye Injection
EXTERNAL JUGULAR VEIN RETURN
Cm.
0 1 2 3 4 5 6 7 8 9 10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Cm.

Figure 30.

CHAPTER IV

SUMMARY AND CONCLUSIONS

Dogs subjected to ventilatory impairment show a rise in pCO_2, and a fall in both pH and pO_2. At a variable period of time from introducing ventilatory impairment the pCO_2 value, numerically, becomes greater than the pO_2 value. The point at which this occurs we have defined as "crossing" and serves as the point at which we have introduced partial cardiopulmonary bypass, as assist for respiratory distress, in most of our studies. Once "crossing" has occurred the time to death has some predictability (48 minutes with a standard deviation of 8.92 minutes).

With ventilatory impairment and institution of partial cardiopulmonary bypass of 30 cc. blood flow per kilogram body weight at the time of "crossing", significant prolongation of life is obtained (Table III).

Prophylactic oxygenation or oxygenation via partial cardiopulmonary bypass instituted at the time of initiating ventilatory impairment shows a marked prolongation of life. This situation has no clinical application but was assessed, as many workers, in the field of assisted circulation for respiratory distress, assess their preparation in such a manner. The lack of validity of using this system has been clearly shown.

Partial cardiopulmonary bypass utilizing high inferior vena caval drainage and either femoral artery, axillary artery, or aortic root return (veno-arterial bypass) or external jugular vein (veno-veno bypass) return were assessed as regards to cerebral pO_2 tension responses with the polarographic microelectrode technique. This electrode was imbedded in the left cerebral hemisphere with tensions

being recorded on a Beckman 160 Gas Analyzer.

Corroboration of this data was obtained by means of Cardio-green (Indocyanine green) dye distribution studies using a Beckman Cardiodensitometer. Dye dilution curves were obtained at both carotid and femoral artery levels.

Cerebral tissue pO_2 tension is noted to fall quickly with asphyxia. Partial cardiopulmonary bypass instituted at the time of "crossing" of the blood gases and utilizing a femoral artery return has very little effect on the falling cerebral tissue pO_2 tension. This results from an absence of newly oxygenated blood from the pump-oxygenator system reaching levels above the aortic root and may be confirmed by dye-dilution curves obtained from the labelled pump-oxygenator blood.

Tall-peaked curves, indicating high concentrations of dye (which indicates a high percentage of pump-oxygenator blood), are obtained at the femoral artery level. Low-peaked or absent curves, indicating low or no concentration of the dye (which indicates little or no pump-oxygenator blood), are obtained at the carotid artery level.

It appears, with a partial cardiopulmonary bypass flow of 30 cc/kg. body weight, pump-oxygenator blood flow is opposed by that portion of the cardiac output directed down the aorta to the extent that none of the pump-oxygenator blood appears above the level of the aortic arch. The implication is that pump-oxygenator blood is directed primarily down the femoral artery not serving as the pump-oxygenator return site.

In sharp contrast to the femoral artery return type of partial cardiopulmonary bypass, right axillary artery return halts the falling pO_2 of cerebral tissue associated with asphyxia. Shortly following initiation of partial cardiopulmonary bypass, a marked improvement to, and in some cases beyond the pre-asphyxia level is noted in the cerebral tissue pO_2 tensions.

Dye distribution studies indicate a cerebral distribution of almost all the pump-oxygenator blood with a right axillary artery return route bypass. The explanation for this is based on the anatomical arrangements of the great vessels of the aortic arch and was discussed in Chapter III.

Partial cardiopulmonary bypass with either aortic arch or external jugular vein return results in an adequate cerebral tissue pO_2 tension response following asphyxia. The overall rise in cerebral perfusion is much the same as noted with an axillary artery return but the time required to achieve similar levels is longer. The possibility exists that tissue saturation with O_2 takes longer because the amount of O_2 being supplied to this area, with aortic root or external jugular vein return bypass circuits, is only slightly greater than the immediate metabolic demands and therefore, little excess of O_2 remains to pay off the tissue O_2 debt. With a right axillary return, the amount of O_2 supplied may be markedly in excess of tissue demands, consequently only a short period is required to pay off this debt and this is reflected in a more immediate response to the cerebral tissue pO_2 electrode.

There does not appear to be any great difference between the aortic root and external jugular vein return bypasses as confirmed by cerebral tissue pO_2 tension responses or dye dilution curves. These two bypass returns appear to be the systems of choice for generalized oxygen distribution, whereas a right axillary artery return benefits, primarily, those clinical states requiring immediate and greater cerebral tissue oxygenation.

Long-term oxygenation of all body tissues could be satisfactorily met by either a veno-venous bypass (external jugular vein return) or a veno-arterial bypass (aortic root return). In those patients expected to be perfused for days, veno-venous bypass would have advantages particularly as regards to hemolysis. The return flow into a system of lower pressures greatly reduces the level of red and white cell destruction. Turbulence is reduced with an anterograde type of return such as occurs with a veno-venous bypass. Retrograde return, as in the arterial return systems, greatly increases the amount of hemolysis arising in turn because of increased turbulence. This latter type of return also increases the work-load of the heart by opposing normal cardiac output.

Femoral artery return has little place in partial cardiopulmonary bypass for respiratory distress except possibly in pulmonary embolism in those patients ultimately going to require embolectomy. Hypotension and high venous pressure, in this situation, facilitate return and drainage from the patient and also afford the advantage of being the site for return in total cardiopulmonary bypass during surgery.

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